CLINICAL STUDY PROTOCOL

NCT Number: NCT02340819

Study Title: A 4-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Study Number: TED-C14-004

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TEDUGLUTIDE (ALX-0600)

A 3-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 1.0

Phase 3

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Protocol v1.0: 05 August 2014

SUMMARY

Protocol TED-C14-004

Title of Study: A 3-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 3-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous volume (PN/I.V.) support optimization period; and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF
- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing
- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs
- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:
    - Actual PN/I.V. usage matches prescribed PN/I.V.
    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.
    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.
- Adequate hepatic function:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN
- Adequate renal function:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute
- Adequate pancreatic function:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN

- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study.

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period; and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization may repeat this period (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue in the extension treatment period for up to an additional 24 months (Stage 3) or until teduglutide is commercially available, whichever comes first. (After the approval of marketing

authorization, the study will continue as a post-marketing clinical study in order to continuously provide teduglutide to the subjects until the product is commercially available).

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stage 3: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety – All Stages: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and

changes in urine output (48-hour I/O), body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

SIGNATURE PAGE

Protocol TED-C14-004

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NPS	NPS Pharmaceuticals, Inc.
PI	Principal Investigator
PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

PN/I.V.	Parenteral Nutrition/Intravenous (volume)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Management Team
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde

diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to

exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the US New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous (PN/I.V.) volume in adult subjects with SBS. In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and in the United States (US). The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and in the US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stage 3

For Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity ($AUC_{0–inf}$)
- AUC from zero to the last measurable concentration ($AUC_{0–t}$)
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

2.4 Safety Objectives – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 3-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stage 3).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. reduction and optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

3.2 Extension Treatment Period (Stage 3)

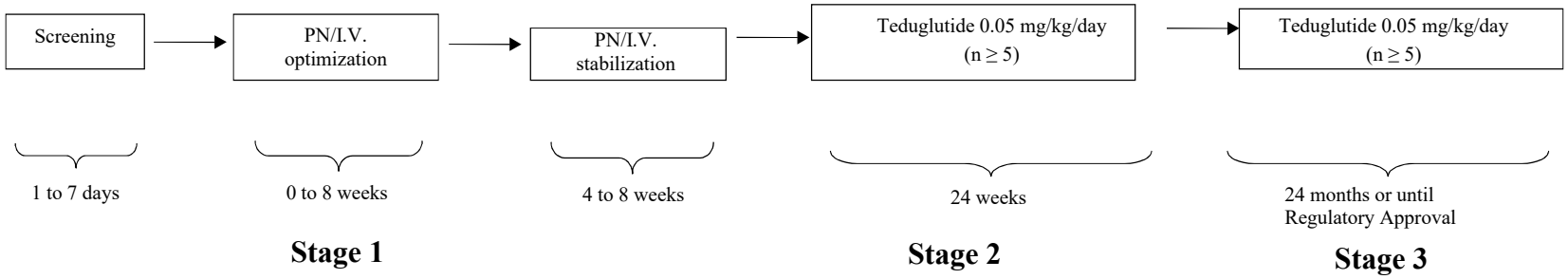
Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2 and will include subjects who complete the main treatment period and who are willing to continue teduglutide treatment. Subjects will continue to receive teduglutide 0.05 mg/kg/day SC for up to an additional 24 months or until teduglutide is commercially available, whichever comes earlier. (After the approval of marketing authorization, the study will continue as a

post-marketing clinical study to continuously provide teduglutide to the subjects until the product is commercially available.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2 and 3 can be found in Table 6-1, Table 6-2 and Table 6-3, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization and treatment periods can be found in Appendix 1 and Appendix 2, respectively, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed
2. Men and women, 16 years of age or older at the time of signing the ICF
3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF
4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs
6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:

    a. Actual PN/I.V. usage matches prescribed PN/I.V.

    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization

    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening
3. Previous use of intravenous glutamine, octreotide, GLP-1 analog , or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening
4. Previous use of teduglutide
5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months
6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening
7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)
9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)
12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years
14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within12 months prior to screening visit
16. Hospital admission, other than scheduled, within 30 days prior to screening
17. Signs of severe hepatic impairment:
    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN
    b. Aspartate aminotransferase (AST) ≥ 5 times ULN
    c. Alanine aminotransferase (ALT) ≥ 5 times ULN
18. Signs of disturbed renal function:
    a. Serum creatinine ≥ 2 times ULN
    b. Creatinine clearance < 50 mL/minute
19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results including:
    a. Serum amylase level ≥ 2 times ULN
    b. Serum lipase level ≥ 2 times ULN
20. Pregnant or lactating women
21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period
22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Evidence of untreated intestinal obstruction or active stenosis
24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
25. Presence of any of the excluded disease states described in Table 4-1.

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
  - o Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
  - o Major surgical interventions (eg, abdominal, vascular)
  - o Crohn's disease flare up
  - o Use of any excluded medication
  - o Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/ Sponsor decision (ie. subject non-compliance with study procedures)

- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of NPS. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the dosing period is in Appendix 2.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. In Stage 3, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during Stage 2 or 3) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:	teduglutide
Added ingredients:	L-histidine, mannitol, monobasic and dibasic sodium phosphate
Route of administration:	SC injection
Dose:	0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and ICCC name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution
- Syringes with needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8°C (36 to 46°F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25° C (59 to 77°F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25°C (36 to 77°F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable

risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets (Appendix 4) and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

Dosing must be performed at least 14 hours prior to antibody testing, which will be performed at baseline and at Weeks 12 and 24 during Period 2 and at Months 6, 12, and 24 during Period 3.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded in the appropriate sections of the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, coumadin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stage 3) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 and 3 of this study are given in Appendix 2 and Appendix 3, respectively.

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms
- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP. Samples for antibody analysis will be drawn at the start of treatment and at the EOT visit (prior to the administration of teduglutide and at least 14 hours after the previous dose). A 6-month follow-up is planned for any subjects testing positive for teduglutide-specific antibodies following the last dose of study drug.
- Changes in urine output (48-hour oral fluid intake/urine output)
- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

Overdose

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the NPS Safety Management Team (SMT) and the sponsor's medical monitor.

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF through the last dose of study drug. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)
    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
    - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
    - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the subject signs the ICF through 30 days after the study drug is completed, the investigator must enter the SAE information into the SAE reporting system and fax supplemental data (eg, medical records or laboratory values, if applicable) to the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor or designee will provide a FAX cover sheet for the investigators in the study reference manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The

investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the study reference manual.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice. If it is determined that there is an unanticipated signal, the NPS SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor or designee will send this summary to the investigators with instructions to provide it to their Institutional Review Board (IRB).

The investigator should also comply with the IRB procedures for reporting any other safety information (ie, autopsy reports).

NPS Pharmaceuticals, Inc. or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Pregnancy Reporting

In the event a subject becomes pregnant during the study, study drug will be discontinued and an SAE form will be completed to capture potential drug exposure during pregnancy. This will be reported within 24 hours of becoming aware of the pregnancy. The subject will be followed up until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion [miscarriage], voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, an additional SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a male subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator (PI) and a supplemental SAE form will be completed to capture the event.

6.2.4 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. A central laboratory will process all samples.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs, if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the

normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2 and Table 6-3.

Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; bicarbonate; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 or early termination during Stage 2 of the study, and at Months 6 and 12, and at the final visit or early termination in Stage 3.

If teduglutide-specific antibodies are detected, subjects may remain in study and will continue to be tested at each visit, as long as there are no concurrent AEs associated with immunogenicity.

Subjects who test positive for teduglutide-specific antibodies at the end of Stage 2 will be allowed to enter Stage 3, as long as there are no concurrent AEs associated with immunogenicity. The presence of teduglutide-specific antibodies will continue to be monitored at every visit until the end of this study. If, at the final visit, the subject is still positive for teduglutide-specific antibodies, the subject will require follow-up blood draws as specified above. If any subject (previously negative for teduglutide antibodies) has specific anti-teduglutide antibodies at the final visit of this study, they will have follow-up blood draws for antibodies at Months 2, 3 and 6 post-study. These may be done at a local laboratory convenient to the subject, however all blood samples will be mailed to the central laboratory for analysis. If a subject's results are negative at 2 successive visits within this time, follow-up may be terminated. If at the end of 6 months the subject is still determined to have

teduglutide-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this follow-up, subjects will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilence database. Collection of AE and/or SAE information may be done via telephone contact.

Teduglutide Concentrations

Teduglutide concentrations will be determined in the blood samples collected for antibody testing, ie, at baseline and at Weeks 12, 24 or early termination during Stage 2 of the study, and at Months 6, 12, and at the final visit or early termination in Stage 3.

6.2.5 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2 and Table 6-3). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.6 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.7 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during Stages 1 and 2 and at the visits specified in Table 6-3 during Stage 3. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring complete I/O, and to record these measurements into the diary. At these times of

48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at any required interim safety visit.

6.2.8 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 3 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.9 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the optimization and stabilization periods and the treatment periods in Stages 2 and 3 of the study.

6.2.10 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the PN/I.V. volume is adjusted as a result of a TEAE that is not related to study drug, then the diary data will not be included in the data analysis. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 and 3 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.11 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.12 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each visit and the details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF.

6.2.13 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and at the final visits of Stage 2 and Stage 3. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.14 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3). Vital signs will include systolic and diastolic blood pressure (mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at the initial visits of Stages 1, 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.15 Electrocardiograms

A 12-lead ECG will be performed at Week 2 during Stage 1, at baseline, Week 4, and at the final visit during Stage 2, and at the first visit (last visit for Stage 2) and at Months 2 and 6 and the final visit during Stage 3. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.16 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1 , Table 6-2, and Table 6-3) for details and scheduling.

6.2.16.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2 and at the end of teduglutide exposure in Stage 3. A colonoscopy is required at the beginning of the study, at the end of the main treatment period and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.16.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures – Stage 3, Table 6-3.

Subjects who drop out of the study prior to the final visit should have all end-of-study procedures done.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period[l] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X	X[a]					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V.		X	X	X	X	X	X[c]
Adverse events			X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs			X	X	X	X	X
Height			X				
Body weight and BMI			X	X	X	X	X[h]
12-lead ECG			X				
Safety laboratory tests			X	X	X	X	
Urine pregnancy test			X				
Interim safety evaluation[i]			[X]	[X]	[X]	[X]	X[j]
Diary		X	X	X	X	X	X
48-hour oral fluid intake[k] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period [l] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
48-hour urine output[k] (Diary)		X	X	X	X	X	X

[X] = possible interim safety evaluation time point (Refer to footnote "i".); BMI = body mass index; ECG = electrocardiogram; PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[l] One re-challenge of the optimization/stabilization is permitted

[a] ICF must be signed before the start of the 48-hour urine output measurements and any other study-related procedures.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for patients with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in patients with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be done 5 to 7 days after any scheduled visit where a PN/I.V. change was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] An interim safety evaluation should be conducted toward the end of the stabilization period to determine that the subject is compliant with Inclusion Criterion 6 (stable PN/I.V.) and Exclusion Criteria 17 (hepatic function) and 18 (renal function).

[k] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment	X								
Physical examination[c]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V.	X[d]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[e]		X	X	X	X	X	X	X
Height	X								X
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X					X			X
PK sampling	X[i]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation[f]			[X][g]	[X]	[X]	[X]	[X]	[X]	
48-hour oral fluid intake[h] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[h] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[j]	X	X	X	X	X	X	X	X	X
Compliance[k]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[d] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[e] This is the second of 2 body weight measurements that will be used to determine drug volume.

[f] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[g] At the Visit 4/Week 2 interim safety visit, laboratory evaluations and 48-hour I/O are not required. These will be assessed only if the PN/I.V. adjustment was tolerated.

[h] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[i] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7.

[j] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will self-inject the study drug at home.

[k] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13	Mo 2/14	Mo 3/15	Mo 4/16	Mo 5/17	Mo 6/18	Mo 7/19	Mo 8/20	Mo 9/21	Mo 10/22	Mo 11/23	Mo 12	Final (Mo 24) (or early termination)
Visit Number:	V1	V2/ 14	V3/ 15	V4/ 16	V5/ 17	V6/ 18	V7/ 19	V8/ 20	V9/ 21	V10/ 22	V11/ 23	V12/ 24	V13	V25
Visit Window (days)		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Eligibility, Informed consent	X													
Medical history, demographics	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[g]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	
Interim safety visit[d]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Diary[e]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[f] (Diary)	X		X		X		X		X		X		X	X
48-hour urine output[f] (Diary)	X		X		X		X		X		X		X	X

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X] = Possible interim safety evaluation time point (Refer to footnote "d".); ECG = electrocardiogram; Mo = month; PN/I.V. = parenteral nutrition/intravenous (support); V = visit
Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 2 visit. Interim (standard of care) visits may be utilized to assess patients' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and final visit; a brief examination will be performed at all other study visits.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily.

[g] An ECG will be taken at Visit 3, but not at Visit 15.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's CRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the CRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The PI or designee will review all CRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the CRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. Paper copies non-CRF data will be signed and dated by the investigator and filed.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is

defined as when the data in the database and the reference values are complete and logical according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit will be performed by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by NPS or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an

incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.

- Change in days per week of PN/I.V. support

- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the upper limit of the 95% CI of the LS mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)

- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stage 3

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg., number and percentage of subjects) for each treatment group. Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point for each treatment group.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment group.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis will also be

performed as secondary/sensitivity analysis. Detailed per-protocol evaluable definitions will be documented in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6th revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the NPS SMT has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1: PN/I.V. OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits**: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.
3. Maintain the PN/I.V. level until the next scheduled optimization visit.
4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated

by targeted urine output of 1.0-2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the NPS Medical Director.

5. **PN/I.V. Stabilization**: Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2: PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD - STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Monitor.

Table A2-1: PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

Table A2-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal

*AND consistent with subject's previous levels prior to study entry.

Note: In combination with Table A2-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. DOSING WEEKS 2, 4, 8, 12, 16, and 20: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected to

evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes**: Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2- 3: Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V..

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition. During the remainder of the study, subjects may undergo 1 additional attempt to reduce volume by at least 10%.

d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3: PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **OPTIMIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Director.

Table A3- 1: PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A1-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of optimized Baseline level up to a clinically appropriate amount (maximum of 30%).

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.
2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.
3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits. Depending on the wellbeing of the subject it is at the discretion of the investigator to abstain from the laboratory safety samples.
4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

* AND consistent with subject's previous levels prior to study entry.

BUN = blood urea nitrogen; ULN = upper limit of normal

Note: In combination with Table A3-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

A. STUDY ORGANIZATION

Sponsor:

NPS Pharmaceuticals, Inc.

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

Medical Monitor (Medical expert of the sponsor):

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[redacted], Clinical Development-GI

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Telephone: [redacted]

Study statistician:

[redacted], MS

[redacted], SAS Programming & Biostatistics

NPS Pharmaceuticals, Inc.

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Data manager:

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[redacted], Data Management

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550 Hills Drive, 3rd Floor

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Pharmacovigilance:

[redacted], RPh, PhD

[redacted], Pharmacovigilance

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

CONTRACT RESEARCH ORGANIZATIONS:

In-Country Clinical Caretaker:

[redacted]

[redacted]

(Contact: [redacted], Pharmaceutical Development Project Division, Regulatory Affairs Department, Regulatory Affairs and Application Group, [redacted])

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Emergency contacts:

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EPS Associates Co., Ltd.

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Coordinating investigator:

[redacted] MD, PhD

[redacted]

[redacted]

[redacted], Japan

B. LIST OF PRINCIPAL INVESTIGATORS AND INVESTIGATIONAL SITES

Investigational Sites	Investigators
[redacted] [redacted] Japan TEL: [redacted]	[redacted]
[redacted] [redacted] Japan TEL: [redacted]	[redacted]
[redacted] [redacted] Japan TEL: [redacted]	[redacted]
[redacted] [redacted] Japan TEL: [redacted]	[redacted]
[redacted] [redacted] Japan TEL: [redacted]	[redacted]

C. LIST OF CLINICAL RESEARCH ASSOCIATES

[redacted], [redacted]

[redacted]

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2-1-3, Korau, Bunkyo-ku,

Tokyo 112-0004, Japan

D. DURATION OF THE STUDY

The proposed duration of the study is from 2014 through 2016. Study start is defined as first patient screened; study end is defined as the hard-lock of the database.

E. PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

_____

Principal Investigator (Print Name)

_____ _____

Principal Investigator (Signature) Date (DD MMM YYYY)

TEDUGLUTIDE (ALX-0600)

A 3-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 2.0

Phase 3

Sponsor: NPS Pharmaceuticals, Inc.

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

USA

Medical Monitor (Medical Expert of the Sponsor):

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[redacted] Clinical Development

In-Country Clinical Caretaker:

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TEL: [redacted] FAX: [redacted]

Protocol v1.0: **05 August 2014**
Protocol v2.0, Amendment 1: **20 August 2014 (administrative amendment)**

SUMMARY

Protocol TED-C14-004

Title of Study: A 3-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 3-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous volume (PN/I.V.) support optimization period; and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF
- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing
- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs
- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:
    - Actual PN/I.V. usage matches prescribed PN/I.V.
    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.
    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.
- Adequate hepatic function:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN
- Adequate renal function:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute
- Adequate pancreatic function:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN

- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study.

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period; and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization may repeat this period (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue in the extension treatment period for up to an additional 24 months (Stage 3) or until teduglutide is commercially available, whichever comes first. (After the approval of marketing

authorization, the study will continue as a post-marketing clinical study in order to continuously provide teduglutide to the subjects until the product is commercially available).

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stage 3: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety – All Stages: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and

changes in urine output (48-hour I/O), body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

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Protocol TED-C14-004

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NPS	NPS Pharmaceuticals, Inc.
PI	Principal Investigator
PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

PN/I.V.	Parenteral Nutrition/Intravenous (volume)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Management Team
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde

diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to

exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the US New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous (PN/I.V.) volume in adult subjects with SBS. In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and in the United States (US). The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and in the US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stage 3

For Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity ($AUC_{0–inf}$)
- AUC from zero to the last measurable concentration ($AUC_{0–t}$)
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

2.4 Safety Objectives – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 3-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stage 3).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. reduction and optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

3.2 Extension Treatment Period (Stage 3)

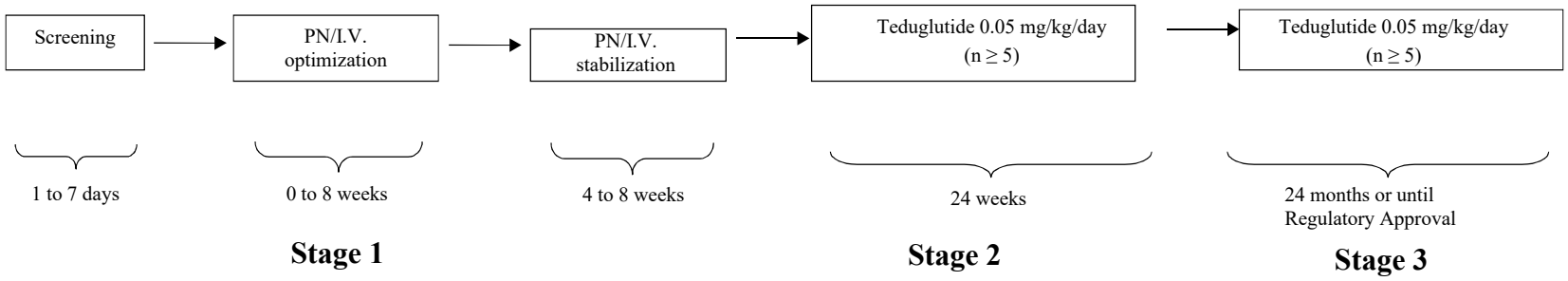
Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2 and will include subjects who complete the main treatment period and who are willing to continue teduglutide treatment. Subjects will continue to receive teduglutide 0.05 mg/kg/day SC for up to an additional 24 months or until teduglutide is commercially available, whichever comes earlier. (After the approval of marketing authorization, the study will continue as a

post-marketing clinical study to continuously provide teduglutide to the subjects until the product is commercially available.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2 and 3 can be found in Table 6-1, Table 6-2 and Table 6-3, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization and treatment periods can be found in Appendix 1 and Appendix 2, respectively, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed
2. Men and women, 16 years of age or older at the time of signing the ICF
3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF
4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs
6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:

    a. Actual PN/I.V. usage matches prescribed PN/I.V.

    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization

    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening
3. Previous use of intravenous glutamine, octreotide, GLP-1 analog , or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening
4. Previous use of teduglutide
5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months
6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening
7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)
9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)
12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years
14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within12 months prior to screening visit
16. Hospital admission, other than scheduled, within 30 days prior to screening
17. Signs of severe hepatic impairment:
    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN
    b. Aspartate aminotransferase (AST) ≥ 5 times ULN
    c. Alanine aminotransferase (ALT) ≥ 5 times ULN
18. Signs of disturbed renal function:
    a. Serum creatinine ≥ 2 times ULN
    b. Creatinine clearance < 50 mL/minute
19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results including:
    a. Serum amylase level ≥ 2 times ULN
    b. Serum lipase level ≥ 2 times ULN
20. Pregnant or lactating women
21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period
22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Evidence of untreated intestinal obstruction or active stenosis
24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
25. Presence of any of the excluded disease states described in Table 4-1.

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
  - o Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
  - o Major surgical interventions (eg, abdominal, vascular)
  - o Crohn's disease flare up
  - o Use of any excluded medication
  - o Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/ Sponsor decision (ie. subject non-compliance with study procedures)

- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of NPS. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the dosing period is in Appendix 2.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. In Stage 3, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during Stage 2 or 3) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:	teduglutide
Added ingredients:	L-histidine, mannitol, monobasic and dibasic sodium phosphate
Route of administration:	SC injection
Dose:	0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and ICCC name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution
- Syringes with needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8°C (36 to 46°F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25° C (59 to 77°F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25°C (36 to 77°F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable

risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

Dosing must be performed at least 14 hours prior to antibody testing, which will be performed at baseline and at Weeks 12 and 24 during Period 2 and at Months 6, 12, and 24 during Period 3.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded in the appropriate sections of the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, coumadin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stage 3) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 and 3 of this study are given in Appendix 2 and Appendix 3, respectively.

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms
- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP. Samples for antibody analysis will be drawn at the start of treatment and at the EOT visit (prior to the administration of teduglutide and at least 14 hours after the previous dose). A 6-month follow-up is planned for any subjects testing positive for teduglutide-specific antibodies following the last dose of study drug.
- Changes in urine output (48-hour oral fluid intake/urine output)
- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

Overdose

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the NPS Safety Management Team (SMT) and the sponsor's medical monitor.

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF through the last dose of study drug. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)
    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
    - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
    - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the subject signs the ICF through 30 days after the study drug is completed, the investigator must enter the SAE information into the SAE reporting system and fax supplemental data (eg, medical records or laboratory values, if applicable) to the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor or designee will provide a FAX cover sheet for the investigators in the study reference manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The

investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the study reference manual.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice. If it is determined that there is an unanticipated signal, the NPS SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor or designee will send this summary to the investigators with instructions to provide it to their Institutional Review Board (IRB).

The investigator should also comply with the IRB procedures for reporting any other safety information (ie, autopsy reports).

NPS Pharmaceuticals, Inc. or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Pregnancy Reporting

In the event a subject becomes pregnant during the study, study drug will be discontinued and an SAE form will be completed to capture potential drug exposure during pregnancy. This will be reported within 24 hours of becoming aware of the pregnancy. The subject will be followed up until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion [miscarriage], voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, an additional SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a male subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator (PI) and a supplemental SAE form will be completed to capture the event.

6.2.4 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. The site's clinical laboratory will centrifuge and send the samples to the central lab, SRL Medisearch Inc. SRL Medisearch will analyze those specimens while sending the citrulline、antibody, and PK samples to NPS headquarters in the U.S.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs, if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the

normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2 and Table 6-3.

Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; total-cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 or early termination during Stage 2 of the study, and at Months 6 and 12, and at the final visit or early termination in Stage 3.

If teduglutide-specific antibodies are detected, subjects may remain in study and will continue to be tested at each visit, as long as there are no concurrent AEs associated with immunogenicity.

Subjects who test positive for teduglutide-specific antibodies at the end of Stage 2 will be allowed to enter Stage 3, as long as there are no concurrent AEs associated with immunogenicity. The presence of teduglutide-specific antibodies will continue to be monitored at every visit until the end of this study. If, at the final visit, the subject is still positive for teduglutide-specific antibodies, the subject will require follow-up blood draws as specified above. If any subject (previously negative for teduglutide antibodies) has specific anti-teduglutide antibodies at the final visit of this study, they will have follow-up blood draws for antibodies at Months 2, 3 and 6 post-study. These may be done at a local laboratory convenient to the subject, however all blood samples will be mailed to the central laboratory for analysis. If a subject's results are negative at 2 successive visits within this time, follow-up may be terminated. If at the end of 6 months the subject is still determined to have

teduglutide-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this follow-up, subjects will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilence database. Collection of AE and/or SAE information may be done via telephone contact.

Teduglutide Concentrations

Teduglutide concentrations will be determined in the blood samples collected for antibody testing, ie, at baseline and at Weeks 12, 24 or early termination during Stage 2 of the study, and at Months 6, 12, and at the final visit or early termination in Stage 3.

6.2.5 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2 and Table 6-3). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.6 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.7 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during Stages 1 and 2 and at the visits specified in Table 6-3 during Stage 3. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring complete I/O, and to record these measurements into the diary. At these times of

48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at any required interim safety visit.

6.2.8 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 3 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.9 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the optimization and stabilization periods and the treatment periods in Stages 2 and 3 of the study.

6.2.10 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the PN/I.V. volume is adjusted as a result of a TEAE that is not related to study drug, then the diary data will not be included in the data analysis. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 and 3 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.11 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.12 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each visit and the details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF.

6.2.13 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and at the final visits of Stage 2 and Stage 3. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.14 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3). Vital signs will include systolic and diastolic blood pressure (mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at the initial visits of Stages 1, 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.15 Electrocardiograms

A 12-lead ECG will be performed at Week 2 during Stage 1, at baseline, Week 4, and at the final visit during Stage 2, and at the first visit (last visit for Stage 2) and at Months 2 and 6 and the final visit during Stage 3. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.16 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1 , Table 6-2, and Table 6-3) for details and scheduling.

6.2.16.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2 and at the end of teduglutide exposure in Stage 3. A colonoscopy is required at the beginning of the study, at the end of the main treatment period and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.16.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures – Stage 3, Table 6-3.

Subjects who drop out of the study prior to the final visit should have all end-of-study procedures done.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period[l] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X	X[a]					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V.		X	X	X	X	X	X[c]
Adverse events			X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs			X	X	X	X	X
Height			X				
Body weight and BMI			X	X	X	X	X[h]
12-lead ECG			X				
Safety laboratory tests			X	X	X	X	
Urine pregnancy test			X				
Interim safety evaluation[i]			[X]	[X]	[X]	[X]	X[j]
Diary		X	X	X	X	X	X
48-hour oral fluid intake[k] (Diary)		X	X	X	X	X	X
48-hour urine output[k] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period [l] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**

[X] = possible interim safety evaluation time point (Refer to footnote "i".); BMI = body mass index; ECG = electrocardiogram; PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[l] One re-challenge of the optimization/stabilization is permitted

[a] ICF must be signed before the start of the 48-hour urine output measurements and any other study-related procedures.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for patients with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in patients with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be done 5 to 7 days after any scheduled visit where a PN/I.V. change was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] An interim safety evaluation should be conducted toward the end of the stabilization period to determine that the subject is compliant with Inclusion Criterion 6 (stable PN/I.V.) and Exclusion Criteria 17 (hepatic function) and 18 (renal function).

[k] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment	X								
Physical examination[c]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V.	X[d]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[e]		X	X	X	X	X	X	X
Height	X								X
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X					X			X
PK sampling	X[i]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation[f]			[X][g]	[X]	[X]	[X]	[X]	[X]	
48-hour oral fluid intake[h] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[h] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[j]	X	X	X	X	X	X	X	X	X
Compliance[k]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[d] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[e] This is the second of 2 body weight measurements that will be used to determine drug volume.

[f] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[g] At the Visit 4/Week 2 interim safety visit, laboratory evaluations and 48-hour I/O are not required. These will be assessed only if the PN/I.V. adjustment was tolerated.

[h] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[i] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7.

[j] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will self-inject the study drug at home.

[k] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13	Mo 2/14	Mo 3/15	Mo 4/16	Mo 5/17	Mo 6/18	Mo 7/19	Mo 8/20	Mo 9/21	Mo 10/22	Mo 11/23	Mo 12	Final (Mo 24) (or early termination)
Visit Number:	V1	V2/ 14	V3/ 15	V4/ 16	V5/ 17	V6/ 18	V7/ 19	V8/ 20	V9/ 21	V10/ 22	V11/ 23	V12/ 24	V13	V25
Visit Window (days)		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Eligibility, Informed consent	X													
Medical history, demographics	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[g]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	
Interim safety visit[d]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Diary [e]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[f] (Diary)	X		X		X		X		X		X		X	X
48-hour urine output[f] (Diary)	X		X		X		X		X		X		X	X

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X] = Possible interim safety evaluation time point (Refer to footnote "d".); ECG = electrocardiogram; Mo = month; PN/I.V. = parenteral nutrition/intravenous (support); V = visit
Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 2 visit. Interim (standard of care) visits may be utilized to assess patients' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and final visit; a brief examination will be performed at all other study visits.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily.

[g] An ECG will be taken at Visit 3, but not at Visit 15.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's CRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the CRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The PI or designee will review all CRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the CRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. Paper copies non-CRF data will be signed and dated by the investigator and filed.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical

according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit will be performed by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by NPS or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all

subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support

- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the upper limit of the 95% CI of the LS mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)

- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stage 3

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg., number and percentage of subjects) for each treatment group. Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point for each treatment group.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment group.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis will also be

performed as secondary/sensitivity analysis. Detailed per-protocol evaluable definitions will be documented in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6^{th} revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the NPS SMT has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1: PN/I.V. OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits**: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.
3. Maintain the PN/I.V. level until the next scheduled optimization visit.
4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated

by targeted urine output of 1.0-2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the NPS Medical Director.

5. **PN/I.V. Stabilization**: Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2: PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD - STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Monitor.

Table A2-1: PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

Table A2-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal

*AND consistent with subject's previous levels prior to study entry.

Note: In combination with Table A2-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. DOSING WEEKS 2, 4, 8, 12, 16, and 20: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected to

evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes**: Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2- 3: Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V..

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition. During the remainder of the study, subjects may undergo 1 additional attempt to reduce volume by at least 10%.

d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3: PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **OPTIMIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Director.

Table A3- 1: PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A1-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of optimized Baseline level up to a clinically appropriate amount (maximum of 30%).

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.
2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.
3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits. Depending on the wellbeing of the subject it is at the discretion of the investigator to abstain from the laboratory safety samples.
4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

* AND consistent with subject's previous levels prior to study entry.

BUN = blood urea nitrogen; ULN = upper limit of normal

Note: In combination with Table A3-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

APPENDIX 4:

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

_____

Principal Investigator (Print Name)

_____ _____

Principal Investigator (Signature) Date (DD MMM YYYY)

TEDUGLUTIDE (ALX-0600)

A 3-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 3.0

Phase 3

Sponsor: NPS Pharmaceuticals, Inc.

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

USA

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Protocol v1.0:	**05 August 2014**
Protocol v2.0, Amendment 1:	**20 August 2014 (administrative amendment)**
Protocol v3.0, Amendment 1 (corrected)	**15 September 2014**

SUMMARY

Protocol TED-C14-004

Title of Study: A 3-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 3-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous volume (PN/I.V.) support optimization period; and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF
- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing
- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs
- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:
    - Actual PN/I.V. usage matches prescribed PN/I.V.
    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.
    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.
- Adequate hepatic function:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN
- Adequate renal function:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute
- Adequate pancreatic function:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN

- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study.

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period; and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization may repeat this period (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue in the extension treatment period for up to an additional 24 months (Stage 3) or until teduglutide is commercially available, whichever comes first. (After the approval of marketing

authorization, the study will continue as a post-marketing clinical study in order to continuously provide teduglutide to the subjects until the product is commercially available).

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stage 3: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety – All Stages: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and

changes in urine output (48-hour I/O), body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

SIGNATURE PAGE

Protocol TED-C14-004

Reviewed and Approved:

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Reviewed:

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[redacted]
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[redacted]
[redacted]Japan

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NPS	NPS Pharmaceuticals, Inc.
PI	Principal Investigator
PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

PN/I.V.	Parenteral Nutrition/Intravenous (volume)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Management Team
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde

diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to

exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the US New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous (PN/I.V.) volume in adult subjects with SBS. In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and in the United States (US). The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and in the US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stage 3

For Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0). Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

2.4 Safety Objectives – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done at the end of the optimization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 3-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stage 3).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. reduction and optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

3.2 Extension Treatment Period (Stage 3)

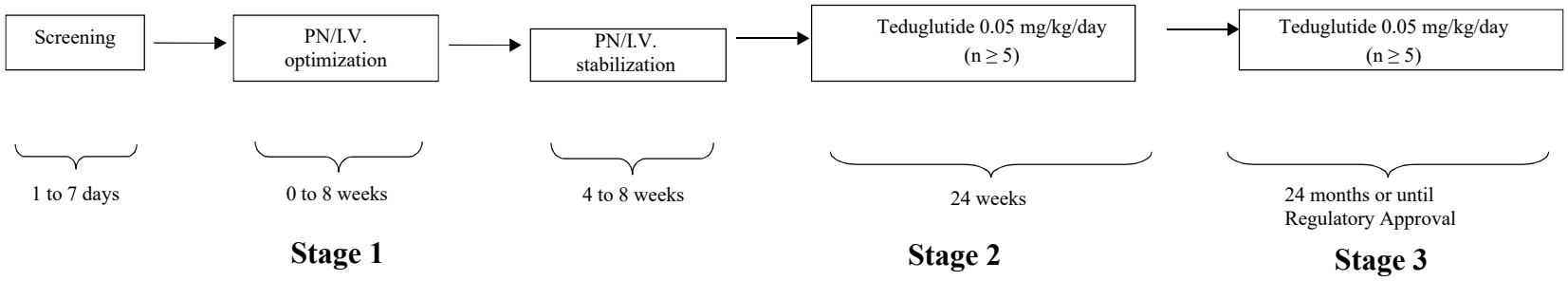
Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2 and will include subjects who complete the main treatment period and who are willing to continue teduglutide treatment. Subjects will continue to receive teduglutide 0.05 mg/kg/day SC for up to an additional 24 months or until teduglutide is commercially available, whichever comes earlier. (After the approval of marketing authorization, the study will continue as a

post-marketing clinical study to continuously provide teduglutide to the subjects until the product is commercially available.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2 and 3 can be found in Table 6-1, Table 6-2 and Table 6-3, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization and treatment periods can be found in Appendix 1 and Appendix 2, respectively, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed
2. Men and women, 16 years of age or older at the time of signing the ICF
3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF
4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs
6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:

    a. Actual PN/I.V. usage matches prescribed PN/I.V.

    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization

    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening
3. Previous use of intravenous glutamine, octreotide, GLP-1 analog , or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening
4. Previous use of teduglutide
5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months
6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening
7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)
9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)
12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years
14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within12 months prior to screening visit
16. Hospital admission, other than scheduled, within 30 days prior to screening
17. Signs of severe hepatic impairment:
    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN
    b. Aspartate aminotransferase (AST) ≥ 5 times ULN
    c. Alanine aminotransferase (ALT) ≥ 5 times ULN
18. Signs of disturbed renal function:
    a. Serum creatinine ≥ 2 times ULN
    b. Creatinine clearance < 50 mL/minute
19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results including:
    a. Serum amylase level ≥ 2 times ULN
    b. Serum lipase level ≥ 2 times ULN
20. Pregnant or lactating women
21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period
22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Evidence of untreated intestinal obstruction or active stenosis
24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
25. Presence of any of the excluded disease states described in Table 4-1.

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
  - o Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
  - o Major surgical interventions (eg, abdominal, vascular)
  - o Crohn's disease flare up
  - o Use of any excluded medication
  - o Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/ Sponsor decision (ie. subject non-compliance with study procedures)

- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of NPS. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the dosing period is in Appendix 2.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. In Stage 3, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during Stage 2 or 3) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:	teduglutide
Added ingredients:	L-histidine, mannitol, monobasic and dibasic sodium phosphate
Route of administration:	SC injection
Dose:	0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and ICCC name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution
- Syringes with needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8°C (36 to 46°F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25° C (59 to 77°F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25°C (36 to 77°F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable

risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

Dosing must be performed at least 14 hours prior to antibody testing, which will be performed at baseline and at Weeks 12 and 24 during Period 2 and at Months 6, 12, and 24 during Period 3.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded in the appropriate sections of the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, warfarin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stage 3) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 and 3 of this study are given in Appendix 2 and Appendix 3, respectively.

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms
- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP. Samples for antibody analysis will be drawn at the start of treatment and at the EOT visit (prior to the administration of teduglutide and at least 14 hours after the previous dose). A 6-month follow-up is planned for any subjects testing positive for teduglutide-specific antibodies following the last dose of study drug.
- Changes in urine output (48-hour oral fluid intake/urine output)
- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

Overdose

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the NPS Safety Management Team (SMT) and the sponsor's medical monitor.

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF through the last dose of study drug. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)
    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
    - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
    - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the subject signs the ICF through 30 days after the study drug is completed, the investigator must enter the SAE information into the SAE reporting system and fax supplemental data (eg, medical records or laboratory values, if applicable) to the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor or designee will provide a FAX cover sheet for the investigators in the study reference manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The

investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the study reference manual.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice. If it is determined that there is an unanticipated signal, the NPS SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor or designee will send this summary to the investigators with instructions to provide it to their Institutional Review Board (IRB).

The investigator should also comply with the IRB procedures for reporting any other safety information (ie, autopsy reports).

NPS Pharmaceuticals, Inc. or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Pregnancy Reporting

In the event a subject becomes pregnant during the study, study drug will be discontinued and an SAE form will be completed to capture potential drug exposure during pregnancy. This will be reported within 24 hours of becoming aware of the pregnancy. The subject will be followed up until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion [miscarriage], voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, an additional SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a male subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator (PI) and a supplemental SAE form will be completed to capture the event.

6.2.4 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. The site's clinical laboratory will centrifuge and send the samples to the central lab, SRL Medisearch Inc. SRL Medisearch will analyze those specimens while sending the citrulline、antibody, and PK samples to NPS headquarters in the U.S.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs, if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the

normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2 and Table 6-3.

Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; total-cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 or early termination during Stage 2 of the study, and at Months 6 and 12, and at the final visit or early termination in Stage 3.

If teduglutide-specific antibodies are detected, subjects may remain in study and will continue to be tested at each visit, as long as there are no concurrent AEs associated with immunogenicity.

Subjects who test positive for teduglutide-specific antibodies at the end of Stage 2 will be allowed to enter Stage 3, as long as there are no concurrent AEs associated with immunogenicity. The presence of teduglutide-specific antibodies will continue to be monitored at every visit until the end of this study. If, at the final visit, the subject is still positive for teduglutide-specific antibodies, the subject will require follow-up blood draws as specified above. If any subject (previously negative for teduglutide antibodies) has specific anti-teduglutide antibodies at the final visit of this study, they will have follow-up blood draws for antibodies at Months 2, 3 and 6 post-study. These may be done at a local laboratory convenient to the subject, however all blood samples will be mailed to the central laboratory for analysis. If a subject's results are negative at 2 successive visits within this time, follow-up may be terminated. If at the end of 6 months the subject is still determined to have

teduglutide-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this follow-up, subjects will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilence database. Collection of AE and/or SAE information may be done via telephone contact.

Teduglutide Concentrations

Teduglutide concentrations will be determined in the blood samples collected for antibody testing, ie, at baseline and at Weeks 12, 24 or early termination during Stage 2 of the study, and at Months 6, 12, and at the final visit or early termination in Stage 3.

6.2.5 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2 and Table 6-3). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.6 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.7 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during Stages 1 and 2 and at the visits specified in Table 6-3 during Stage 3. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring complete I/O, and to record these measurements into the diary. At these times of

48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at any required interim safety visit.

6.2.8 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 2 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.9 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the optimization and stabilization periods and the treatment periods in Stages 2 and 3 of the study.

6.2.10 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the PN/I.V. volume is adjusted as a result of a TEAE that is not related to study drug, then the diary data will not be included in the data analysis. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 and 3 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.11 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.12 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each visit and the details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF.

6.2.13 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and at the final visits of Stage 2 and Stage 3. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.14 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3). Vital signs will include systolic and diastolic blood pressure (mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at the initial visits of Stages 1, 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.15 Electrocardiograms

A 12-lead ECG will be performed at Week 2 during Stage 1, at baseline, Week 4, and at the final visit during Stage 2, and at the first visit (last visit for Stage 2) and at Months 2 and 6 and the final visit during Stage 3. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.16 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1 , Table 6-2, and Table 6-3) for details and scheduling.

6.2.16.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2 and at the end of teduglutide exposure in Stage 3. A colonoscopy is required at the beginning of the study, at the end of the main treatment period and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.16.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures – Stage 3, Table 6-3.

Subjects who drop out of the study prior to the final visit should have all end-of-study procedures done.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period[1] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X	X[a]					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V.		X	X	X	X	X	X[c]
Adverse events			X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs			X	X	X	X	X
Height			X				
Body weight and BMI			X	X	X	X	X[h]
12-lead ECG			X				
Safety laboratory tests			X	X	X	X	
Urine pregnancy test			X				
Interim safety evaluation[i]			[X]	[X]	[X]	[X]	X[j]
Diary		X	X	X	X	X	X
48-hour oral fluid intake[k] (Diary)		X	X	X	X	X	X
48-hour urine output[k] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period [l] (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**

[X] = possible interim safety evaluation time point (Refer to footnote "i".); BMI = body mass index; ECG = electrocardiogram; PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[l] One re-challenge of the optimization/stabilization is permitted

[a] ICF must be signed before the start of the 48-hour urine output measurements and any other study-related procedures.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for patients with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in patients with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be done 5 to 7 days after any scheduled visit where a PN/I.V. change was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] An interim safety evaluation should be conducted toward the end of the stabilization period to determine that the subject is compliant with Inclusion Criterion 6 (stable PN/I.V.) and Exclusion Criteria 17 (hepatic function) and 18 (renal function).

[k] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment	X								
Physical examination[c]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V.	X[d]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[e]		X	X	X	X	X	X	X
Height	X								X
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X					X			X
PK sampling	X[i]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation[f]			[X][g]	[X]	[X]	[X]	[X]	[X]	
48-hour oral fluid intake[h] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[h] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[j]	X	X	X	X	X	X	X	X	X
Compliance[k]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[d] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[e] This is the second of 2 body weight measurements that will be used to determine drug volume.

[f] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[g] At the Visit 4/Week 2 interim safety visit, laboratory evaluations and 48-hour I/O are not required. These will be assessed only if the PN/I.V. adjustment was tolerated.

[h] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[i] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7.

[j] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will self-inject the study drug at home.

[k] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13	Mo 2/14	Mo 3/15	Mo 4/16	Mo 5/17	Mo 6/18	Mo 7/19	Mo 8/20	Mo 9/21	Mo 10/22	Mo 11/23	Mo 12	Final (Mo 24) (or early termination)
Visit Number:	V1	V2/ 14	V3/ 15	V4/ 16	V5/ 17	V6/ 18	V7/ 19	V8/ 20	V9/ 21	V10/ 22	V11/ 23	V12/ 24	V13	V25
Visit Window (days)		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Eligibility, Informed consent	X													
Medical history, demographics	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[g]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	
Interim safety visit[d]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Diary [e]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[f] (Diary)	X		X		X		X		X		X		X	X
48-hour urine output[f] (Diary)	X		X		X		X		X		X		X	X

Table 6-3: Schedule of Evaluations and Procedures – Stage 3 (Extension)

Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X] = Possible interim safety evaluation time point (Refer to footnote "d".); ECG = electrocardiogram; Mo = month; PN/I.V. = parenteral nutrition/intravenous (support); V = visit
Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 2 visit. Interim (standard of care) visits may be utilized to assess patients' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and final visit; a brief examination will be performed at all other study visits.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily.

[g] An ECG will be taken at Visit 3, but not at Visit 15.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's CRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the CRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The PI or designee will review all CRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the CRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. Paper copies non-CRF data will be signed and dated by the investigator and filed.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical

according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit will be performed by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by NPS or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all

subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support

- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the upper limit of the 95% CI of the LS mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)

- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stage 3

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety – All Stages

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg., number and percentage of subjects) for each treatment group. Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point for each treatment group.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment group.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis will also be

performed as secondary/sensitivity analysis. Detailed per-protocol evaluable definitions will be documented in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6th revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the NPS SMT has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1: PN/I.V. OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits**: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.
3. Maintain the PN/I.V. level until the next scheduled optimization visit.
4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated

by targeted urine output of 1.0-2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the NPS Medical Director.

5. **PN/I.V. Stabilization**: Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2: PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD - STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Monitor.

Table A2-1: PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

Table A2-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal

*AND consistent with subject's previous levels prior to study entry.

Note: In combination with Table A2-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. DOSING WEEKS 2, 4, 8, 12, 16, and 20: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected to

evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes**: Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2- 3: Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V..

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition. During the remainder of the study, subjects may undergo 1 additional attempt to reduce volume by at least 10%.

d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3: PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **OPTIMIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Director.

Table A3- 1: PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A1-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of optimized Baseline level up to a clinically appropriate amount (maximum of 30%).

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.
2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.
3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits. Depending on the wellbeing of the subject it is at the discretion of the investigator to abstain from the laboratory safety samples.
4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

* AND consistent with subject's previous levels prior to study entry.

BUN = blood urea nitrogen; ULN = upper limit of normal

Note: In combination with Table A3-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

APPENDIX 4:

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

_____

Principal Investigator (Print Name)

_____ _____

Principal Investigator (Signature) Date (DD MMM YYYY)

TEDUGLUTIDE (ALX-0600)

A 3-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 4.0

Phase 3

Sponsor:

NPS Pharmaceuticals, Inc.

550 Hills Drive, 3rd Floor

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Protocol v1.0:	**05 August 2014**
Protocol v2.0, Amendment 1:	**20 August 2014 (administrative amendment)**
Protocol v3.0, Amendment 1 (corrected)	**15 September 2014**
Protocol v4.0, Amendment 2	**03 March 2015**

SUMMARY

Protocol TED-C14-004

Title of Study: A 3-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 3-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous volume (PN/I.V.) support optimization period (if required); and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF
- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing
- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs
- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:
    - Actual PN/I.V. usage matches prescribed PN/I.V.
    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.
    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.
- Adequate hepatic function at the time of stabilization:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN
- Adequate renal function at the time of stabilization:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute (only in subjects with a known history of creatinine clearance < 50 mL/min)
- Adequate pancreatic function at the time of stabilization:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN

- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study.

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period (if required); and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization may repeat this period (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue in the extension treatment period for up to an additional 24 months (Stage 3) or until teduglutide is commercially available, whichever comes first. (After the approval of marketing

authorization, the study will continue as a post-marketing clinical study in order to continuously provide teduglutide to the subjects until the product is commercially available).

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stage 3: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and changes in 48-hour urine output, body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

SIGNATURE PAGE

Protocol TED-C14-004

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NPS	NPS Pharmaceuticals, Inc.
PI	Principal Investigator
PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

PN/I.V.	Parenteral Nutrition/Intravenous (volume)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Management Team
SUSAR	Suspected, unexpected, serious, adverse reaction
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde

diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to

exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the US New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous (PN/I.V.) volume in adult subjects with SBS. In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and in the United States (US). The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and in the US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stage 3

For Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity ($AUC_{0–inf}$)
- AUC from zero to the last measurable concentration ($AUC_{0–t}$)
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

2.4 Safety Objectives

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 3-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stage 3).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

3.2 Extension Treatment Period (Stage 3)

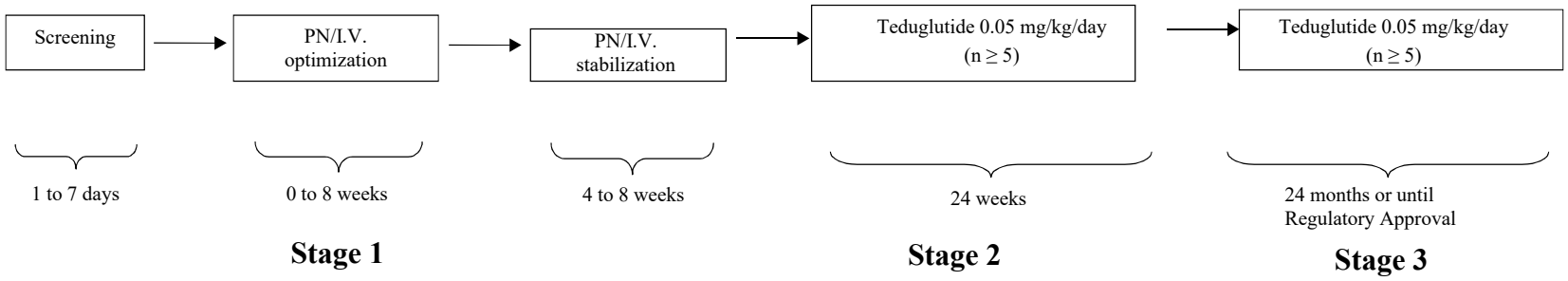
Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2 and will include subjects who complete the main treatment period and who are willing to continue teduglutide treatment. Subjects will continue to receive teduglutide 0.05 mg/kg/day SC for up to an additional 24 months or until teduglutide is commercially available, whichever comes earlier. (After the approval of marketing authorization, the study will continue as a

post-marketing clinical study to continuously provide teduglutide to the subjects until the product is commercially available.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2 and 3 can be found in Table 6-1, Table 6-2 and Table 6-3, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization and treatment periods can be found in Appendix 1 and Appendix 2, respectively, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed
2. Men and women, 16 years of age or older at the time of signing the ICF
3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF
4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.
5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs
6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:

    a. Actual PN/I.V. usage matches prescribed PN/I.V.

    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization

    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening
3. Previous use of intravenous glutamine, octreotide, GLP-1 analog , or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening
4. Previous use of teduglutide
5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months
6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening
7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)
9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)
12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years
14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within12 months prior to screening visit
16. Hospital admission, other than scheduled, within 30 days prior to screening
17. Signs of severe hepatic impairment at time of stabilization:
    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN
    b. Aspartate aminotransferase (AST) ≥ 5 times ULN
    c. Alanine aminotransferase (ALT) ≥ 5 times ULN
18. Signs of disturbed renal function at time of stabilization:
    a. Serum creatinine ≥ 2 times ULN
    b. Creatinine clearance < 50 mL/minute*

    *Only applies to subjects with a known history of creatinine clearance (CrCl) < 50 mL/min who then will be required to have a CrCl ≥ 50 mL in order to participate in the study. If a CrCl cannot be measured, an estimated glomerular filtration rate (eGFR) may be calculated.
19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results at time of stabilization including:
    a. Serum amylase level ≥ 2 times ULN
    b. Serum lipase level ≥ 2 times ULN
20. Pregnant or lactating women
21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period
22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
23. Evidence of untreated intestinal obstruction or clinically significant active stenosis
24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
25. Presence of any of the excluded disease states described in Table 4-1.

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
  - o Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
  - o Major surgical interventions (eg, abdominal, vascular)
  - o Crohn's disease flare up
  - o Use of any excluded medication
  - o Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/ Sponsor decision (ie. subject non-compliance with study procedures)

- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of NPS. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the dosing period is in Appendix 2.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. In Stage 3, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during Stage 2 or 3) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:	teduglutide
Added ingredients:	L-histidine, mannitol, monobasic and dibasic sodium phosphate
Route of administration:	SC injection
Dose:	0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and In-Country Clinical Caretaker name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution
- Syringes with needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8°C (36 to 46°F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25° C (59 to 77°F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25°C (36 to 77°F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable

risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

Dosing must be performed at least 14 hours prior to antibody testing, which will be performed at Baseline and at Weeks 12 and 24 during Stage 2 and at Months 6, 12, 18, and 24 or early termination during Stage 3, or at early termination.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded in the appropriate sections of the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, warfarin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stage 3) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 and 3 of this study are given in Appendix 2 and Appendix 3, respectively.

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms
- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP. Samples for antibody analysis will be drawn at the start of treatment and at the EOT visit (prior to the administration of teduglutide and at least 14 hours after the previous dose). A 6-month follow-up is planned for any subjects testing positive for teduglutide-specific antibodies following the last dose of study drug.
- Changes in urine output (48-hour oral fluid intake/urine output)
- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

Overdose

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the NPS Safety Management Team (SMT) and the sponsor's medical monitor.

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF through the last dose of study drug. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)
    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
    - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
    - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the subject signs the ICF through 30 days after the study drug is completed, the investigator must enter the SAE information into the SAE reporting system and fax supplemental data (eg, medical records or laboratory values, if applicable) to the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor or designee will provide a FAX cover sheet for the investigators in the study reference manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The

investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the study reference manual.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice. If it is determined that there is an unanticipated signal, the NPS SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor or designee will send this summary to the investigators with instructions to provide it to their Institutional Review Board (IRB).

The investigator should also comply with the IRB procedures for reporting any other safety information (ie, autopsy reports).

NPS Pharmaceuticals, Inc. or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Pregnancy Reporting

In the event a subject becomes pregnant during the study, study drug will be discontinued and an SAE form will be completed to capture potential drug exposure during pregnancy. This will be reported within 24 hours of becoming aware of the pregnancy. The subject will be followed up until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion [miscarriage], voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, an additional SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a male subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator (PI) and a supplemental SAE form will be completed to capture the event.

6.2.4 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. The site's clinical laboratory will centrifuge and send the samples to the central lab, SRL Medisearch Inc. to be analyzed. Citrulline, antibody, and PK samples will be handled according to procedures specified in the laboratory manual.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs, if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2, and Table 6-3.

Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; total-cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 or early termination during Stage 2 of the study, and at Months 6, 12, 18, and 24 or early termination during Stage 3.

If teduglutide-specific antibodies are detected, subjects may remain in study and will continue to be tested at each visit, as long as there are no concurrent AEs associated with immunogenicity.

Subjects who test positive for teduglutide-specific antibodies at the end of Stage 2 will be allowed to enter Stage 3, as long as there are no concurrent AEs associated with immunogenicity. The presence of teduglutide-specific antibodies will continue to be monitored at every visit until the end of this study. If, at the final visit, the subject is still positive for teduglutide-specific antibodies, the subject will require follow-up blood draws as specified above. If any subject (previously negative for teduglutide antibodies) has specific anti-teduglutide antibodies at the final visit of this study, they will have follow-up blood draws for antibodies at Months 2, 3 and 6 post-study. These may be done at a local laboratory

convenient to the subject, however all blood samples will be mailed to the central laboratory for analysis. If a subject's results are negative at 2 successive visits within this time, follow-up may be terminated. If at the end of 6 months the subject is still determined to have teduglutide-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this follow-up, subjects will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilence database. Collection of AE and/or SAE information may be done via telephone contact.

Teduglutide Concentrations

Teduglutide concentrations will be determined in the blood samples collected for antibody testing, ie, at Baseline and at Weeks 12, 24 or early termination during Stage 2 of the study, and at Months 6, 12, 18, and 24 or early termination during Stage 3.

6.2.5 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2 and Table 6-3). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.6 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.7 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during

Stages 1 and 2 and at the visits specified in Table 6-3 during Stage 3. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring complete I/O, and to record these measurements into the diary. At these times of 48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at any required interim safety visit.

6.2.8 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 2 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.9 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the screening, optimization and stabilization periods, and the treatment periods in Stages 2 and 3 of the study. Diaries should be distributed initially at the time the subject signs consent. Subjects should be instructed to record the 48-hour oral intake/urinary output prior to the screening visit (Visit 1.0) in order to assess their eligibility for stabilization.

6.2.10 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the PN/I.V. volume is adjusted as a result of a TEAE that is not related to study drug, then the diary data will not be included in the data analysis. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN/I.V. volume adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 and 3 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.11 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.12 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each visit and the details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF.

6.2.13 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and at the final visits of Stage 2 and Stage 3. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.14 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3). Vital signs will include systolic and diastolic blood pressure (mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at screening and at the initial visits of Stages 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.15 Electrocardiograms

A 12-lead ECG will be performed during screening, at baseline, Week 4, and at the final visit during Stage 2, and at the first visit (last visit for Stage 2) and at Months 2, 6, 12, 18, and 24 or early termination during Stage 3. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or

designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.16 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1 , Table 6-2, and Table 6-3) for details and scheduling.

6.2.16.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2 and at the end of teduglutide exposure in Stage 3. A colonoscopy is required at the beginning of the study, at the end of the main treatment period and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.16.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$

- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures – Stage 3, Table 6-3.

Subjects who drop out of the study prior to the final visit should have all end-of-study procedures done.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X[a]	X					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V.		X	X	X	X	X	X[c]
Adverse events		X	X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs		X	X	X	X	X	X
Height		X					
Body weight and BMI		X	X	X	X	X	X[h]
12-lead ECG		X					
Safety laboratory tests		X	X	X	X	X	X
Urine pregnancy test		X					
Interim safety evaluation		[X][i]	[X][i]	[X][i]	[X][i]	[X][i]	
Diary	X[a]	X	X	X	X	X	X
Review 48-hour oral fluid intake[j] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Review 48-hour urine output[j] (Diary)		X	X	X	X	X	X
Optimization assessment[k]		X	X	X	X	X	

BMI = body mass index; ECG = electrocardiogram; GI = gastrointestinal; ICF = Informed Consent Form; PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

Note: One repeat of the optimization/stabilization periods combined is permitted.

[a] The ICF is to be distributed to the subject for review. Once the ICF has been signed by the subject, the diary should be given to the subject in order to record the 48-hour intake/output measurements. No study-related procedures are to be performed unless the ICF has been signed.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for subjects with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in subjects with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be assessed **5 to 7 days** after any scheduled visit **only if a PN/I.V. change** was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[k] The optimization assessment should be made by reviewing the 48-hour oral fluid intake and urine output from the Diary and assessing whether the subject meets the optimization criteria as described in the protocol.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment[c]	X								
Physical examination[d]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V.	X[e]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[f]		X	X	X	X	X	X	X
Height	X								
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X					X			X
PK sampling	X[j]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation			[X][g, h]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	
48-hour oral fluid intake[i] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[i] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[k]	X	X	X	X	X	X	X	X	X
Compliance[l]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] Subjects with active Crohn's disease are excluded from the study participation, therefore endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease.

[d] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[e] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[f] This is the second of 2 body weight measurements that will be used to determine drug volume.

[g] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[h] At the Visit 4/Week 2 interim safety visit, laboratory evaluations and 48-hour I/O are not required. These will be assessed only if the PN/I.V. adjustment was tolerated.

[i] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[j] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

[k] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will then self-inject the study drug at home.

[l] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13[b]	Mo 2/14	Mo 3/15[b]	Mo 4/16	Mo 5/17[b]	Mo 6/18	Mo 7/19[b]	Mo 8/20	Mo 9/21[b]	Mo 10/22	Mo 11/23[b]	Mo 12	Final (Mo 24) (or early termi-nation)
Visit Number:	**V1**	**V2/ 14**	**V3/ 15**	**V4/ 16**	**V5/ 17**	**V6/ 18**	**V7/ 19**	**V8/ 20**	**V9/ 21**	**V10/ 22**	**V11/ 23**	**V12/ 24**	**V13**	**V25**
Visit Window (days)		**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Eligibility, Informed consent	X													
Medical history, demographics	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight and BMI	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[g]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Teduglutide concentration and antibodies to teduglutide and *E. coli* protein	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	
Interim safety visit	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]
Diary[e]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[f] (Diary)	X		X		X		X		X		X		X	X
48-hour urine output[f] (Diary)	X		X		X		X		X		X		X	X

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X] = Possible interim safety evaluation time point (Refer to footnote "d".); BMI = body mass index; ECG = electrocardiogram; L = liter; Mo = month; PN/I.V. = parenteral nutrition/intravenous (support); V = visit

Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 1 visit. Interim (standard of care) visits may be utilized to assess sunjects' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and final visit; a brief examination will be performed at all other study visits.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily.

[g] An ECG will be taken at Visit 3, but not at Visit 15.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's CRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the CRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The PI or designee will review all CRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the CRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. Paper copies non-CRF data will be signed and dated by the investigator and filed.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical

according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit will be performed by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by NPS or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all

subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support

- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the upper limit of the 95% CI of the LS mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)

- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stage 3

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg., number and percentage of subjects) for each treatment group. Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point for each treatment group.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment group.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis will also be

performed as secondary/sensitivity analysis. Detailed per-protocol evaluable definitions will be documented in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6^{th} revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the NPS SMT has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1: PN/I.V. OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits**: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.
2. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.
3. Maintain the PN/I.V. level until the next scheduled optimization visit.

4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated by targeted urine output of 1.0 to 2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the sponsor's Medical Monitor.
5. **PN/I.V. Stabilization**: Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2: PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD - STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Monitor.

Table A2-1: PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. – parenteral nutrition/intravenous (volume)

Table A2-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal

*AND consistent with subject's previous levels prior to study entry.

Note: In combination with Table A2-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. DOSING WEEKS 2, 4, 8, 12, 16, and 20: Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off

PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected to evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes**: Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations**: If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2- 3: Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume).
[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

    a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V..

b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition. During the remainder of the study, subjects may undergo 1 additional attempt to reduce volume by at least 10%.

d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3: PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **OPTIMIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the NPS Medical Director.

Table A3- 1: PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-1), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of optimized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume)

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.
2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.
3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits. Depending on the wellbeing of the subject it is at the discretion of the investigator to abstain from the laboratory safety samples.
4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal

* AND consistent with subject's previous levels prior to study entry.

Note: In combination with Table A3-1, any one of the above criteria determines dehydration.

Note: If weight gain of ≥1.5 kg, request physician review.

APPENDIX 4:

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

Principal Investigator (Print Name)

Principal Investigator (Signature) Date (DD MMM YYYY)

TEDUGLUTIDE (ALX-0600)

A 3-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 5.0

Phase 3

Sponsor:

NPS Pharmaceuticals, Inc.*

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

USA

(*NPS was acquired by Shire, Inc. on 21 February 2015)

Medical Monitor (Medical Expert of the Sponsor):

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Protocol v1.0:	**05 August 2014**
Protocol v2.0, Amendment 1:	**20 August 2014 (administrative amendment)**
Protocol v3.0, Amendment 1 (corrected):	**15 September 2014**
Protocol v4.0, Amendment 2:	**03 March 2015**
Protocol v5.0, Amendment 3:	**17 November 2015**

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the sponsor's Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the sponsor's Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover) and below. A copy of this form must also be sent to the sponsor's Medical Monitor by fax or e-mail using the details below.

Global Pharmacovigilance and Risk Management
E-mail: [redacted]
Fax: [redacted]

[redacted] **MD** [redacted]
Fax: [redacted]
E-mail: [redacted]

SUMMARY

Protocol TED-C14-004

Title of Study: A 3-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 3-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous volume (PN/I.V.) support optimization period (if required); and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF

- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing

- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs

- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:

    - Actual PN/I.V. usage matches prescribed PN/I.V.

    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.

    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

- Adequate hepatic function at the time of stabilization:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN

- Adequate renal function at the time of stabilization:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute (only in subjects with a known history of creatinine clearance < 50 mL/min)

- Adequate pancreatic function at the time of stabilization:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN

- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities

- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome

- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study.

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period (if required); and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization may repeat this period (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue in the extension treatment period for up to an additional 24 months (Stage 3) or until teduglutide is commercially available, whichever comes first. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study in order to continuously provide teduglutide to the subjects until the product is commercially available).

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by

visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.

- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stage 3: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose PK will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and changes in 48-hour urine output, body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

SIGNATURE PAGE

Protocol TED-C14-004

Reviewed and Approved:

[redacted], **MD**
[redacted] &
[redacted] (Study Physician)

[redacted] Signature

[redacted] Date
(DD MMM YYYY)

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients
PN/I.V.	Parenteral Nutrition/Intravenous (volume)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SUSAR	Suspected, unexpected, serious, adverse reaction
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in

mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the United States (US) New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous (PN/I.V.) volume in adult subjects with SBS. In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and the US. The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult

subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stage 3

For Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

2.4 Safety Objectives

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (Stage 3). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 3-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stage 3).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

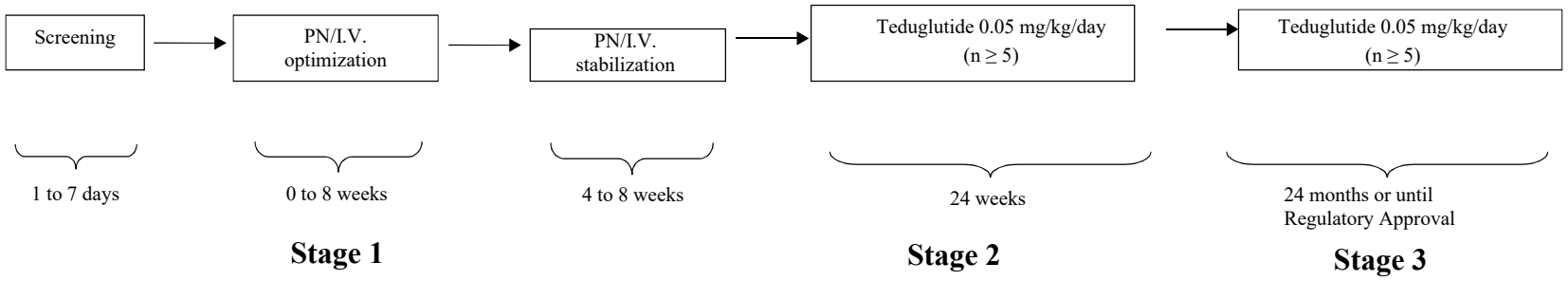
3.2 Extension Treatment Period (Stage 3)

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2 and will include subjects who complete the main treatment period and who are willing to continue teduglutide treatment. Subjects will continue to receive teduglutide 0.05 mg/kg/day SC for up to an additional 24 months or until teduglutide is commercially available, whichever comes earlier. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study to continuously provide teduglutide to the subjects until the product is commercially available.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2 and 3 can be found in Table 6-1, Table 6-2 and Table 6-3, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization and treatment periods can be found in Appendix 1 and Appendix 2, respectively, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed

2. Men and women, 16 years of age or older at the time of signing the ICF

3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF

4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.

5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs

6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:

    a. Actual PN/I.V. usage matches prescribed PN/I.V.

    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization

c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide

2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening

3. Previous use of intravenous glutamine, octreotide, GLP-1 analog, or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening

4. Previous use of teduglutide

5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months

6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening

7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months

8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)

9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome

10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening

11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)

12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair

13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years

14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within 12 months prior to screening visit

16. Hospital admission, other than scheduled, within 30 days prior to screening

17. Signs of severe hepatic impairment at time of stabilization:

    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN

    b. Aspartate aminotransferase (AST) ≥ 5 times ULN

    c. Alanine aminotransferase (ALT) ≥ 5 times ULN

18. Signs of disturbed renal function at time of stabilization:

    a. Serum creatinine ≥ 2 times ULN

    b. Creatinine clearance < 50 mL/minute*

       *Only applies to subjects with a known history of creatinine clearance (CrCl) < 50 mL/min who then will be required to have a CrCl ≥ 50 mL in order to participate in the study. If a CrCl cannot be measured, an estimated glomerular filtration rate (eGFR) may be calculated.

19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results at time of stabilization including:

    a. Serum amylase level ≥ 2 times ULN

    b. Serum lipase level ≥ 2 times ULN

20. Pregnant or lactating women

21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period

22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements

23. Evidence of untreated intestinal obstruction or clinically significant active stenosis

24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results

25. Presence of any of the excluded disease states described in Table 4-1

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Eversmeyerous polypius)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the

procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
    - Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
    - Major surgical interventions (eg, abdominal, vascular)
    - Crohn's disease flare up
    - Use of any excluded medication
    - Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/Sponsor decision (ie, subject non-compliance with study procedures)
- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of the sponsor. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the dosing period is in Appendix 2.

Stage 3 is the long-term extension portion of the study, which will begin immediately following Stage 2. In Stage 3, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day for up to 24 months or until regulatory approval and commercial availability of teduglutide in Japan. (After the approval of marketing authorization, the study will continue as a post-marketing clinical study until the market launch.)

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during Stage 2 or 3) will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:	teduglutide
Added ingredients:	L-histidine, mannitol, monobasic and dibasic sodium phosphate
Route of administration:	SC injection
Dose:	0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and In-Country Clinical Caretaker name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution
- Syringes with needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8^{o}C (36 to 46^{o}F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25^{o} C (59 to 77^{o}F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25^{o}C (36 to 77^{o}F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

Dosing must be performed at least 14 hours prior to antibody testing, which will be performed at Baseline and at Weeks 12 and 24 during Stage 2 and at Months 6, 12, 18, and 24 or early termination during Stage 3, or at early termination.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support (either during optimization or at any time during the Stage 2 or 3 treatment period) will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded in the appropriate sections of the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, warfarin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stage 3) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 and 3 of this study are given in Appendix 2 and Appendix 3, respectively.

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stage 3, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms

- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP (see Table 6-1, Table 6-2, and Table 6-3 for timing)
- Changes in urine output (48-hour oral fluid intake/urine output)
- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

ABUSE, MISUSE, OVERDOSE, AND MEDICATION ERROR

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 6.2.1.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE. The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

- **Overdose** – An accidental or intentional administration of an excessive dose of a product

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF through the last dose of study drug. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)

- Whether the event is continuing

- Frequency (intermittent, continuous)

- Intensity (mild, moderate, severe)

    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities

  - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
  - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required

- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below.
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death

- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

All initial and follow-up SAE reports must be reported by the investigator to the sponsor's Global Pharmacovigilance and Risk Management Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 6.2.1.1) unless they result in an SAE.

The investigator must complete, sign, and date the sponsor's Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source

documents are not to be sent unless requested) and fax or e-mail the form to the sponsor's Global Pharmacovigilance and Risk Management Department. A copy of the sponsor's Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the sponsor's Medical Monitor using the details specified in the emergency contact information section of the protocol.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The sponsor or designee will provide a FAX cover sheet for the investigators.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

- Not related
    - Unrelated to investigational product
- Possibly Related
    - A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.

- Probably Related
    - A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
- Related
    - The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the patient to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

The investigator should also comply with the Institutional Review Board (IRB) procedures for reporting any other safety information (eg, autopsy reports).

The sponsor or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Pregnancy Reporting

In the event a subject becomes pregnant during the study, study drug will be discontinued and an SAE form will be completed to capture potential drug exposure during pregnancy. This will be reported within 24 hours of becoming aware of the pregnancy. The subject will be followed up until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous abortion [miscarriage], voluntary abortion, or therapeutic abortion). If a pregnant subject also experiences an SAE, an additional SAE form will be completed and submitted within 24 hours as discussed above.

In the event a female partner of a male subject becomes pregnant within 30 days after the subject completes the trial and she or the fetus experiences an SAE, the SAE is deemed "suspected" to study drug by the principal investigator (PI) and a supplemental SAE form will be completed to capture the event.

6.2.4 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. The site's clinical laboratory will centrifuge and send the samples to the central lab, SRL Medisearch Inc. to be analyzed. Citrulline, antibody, and PK samples will be handled according to procedures specified in the laboratory manual.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs, if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2, and Table 6-3:

- Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

- Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; total-cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

- Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

- Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

- Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 or early termination during Stage 2 of the study, and at Months 6, 12, 18, and 24 or early termination during Stage 3.

Antibody testing is a 3-part process. If a sample is negative, no further testing is done. If a sample is positive, testing is done for teduglutide-specific antibodies. If these are detected, the titer is derived and neutralizing antibody testing is done. Subjects may remain on treatment and will continue to be tested at each visit as long as there are no concurrent AEs associated with immunogenicity.

Subjects who test positive for teduglutide-specific antibodies at the end of Stage 2 will be allowed to enter Stage 3, as long as there are no concurrent AEs associated with immunogenicity. The presence of teduglutide-specific antibodies will continue to be monitored at every visit where antibody testing is scheduled per protocol.

6.2.5 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2 and Table 6-3). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.6 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.7 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during Stages 1 and 2 and at the visits specified in Table 6-3 during Stage 3. The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring complete I/O, and to record these measurements into the diary. At these times of 48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at any required interim safety visit.

6.2.8 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 2 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.9 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the screening, optimization and stabilization periods, and the treatment periods in Stages 2 and 3 of

the study. Diaries should be distributed initially at the time the subject signs consent. Subjects should be instructed to record the 48-hour oral intake/urinary output prior to the screening visit (Visit 1.0) in order to assess their eligibility for stabilization.

6.2.10 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the PN/I.V. volume is adjusted as a result of a TEAE that is not related to study drug, then the diary data will not be included in the data analysis. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN/I.V. volume adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 and 3 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.11 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.12 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each visit and the details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF.

6.2.13 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and at the final visits of Stage 2 and Stage 3. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.14 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3). Vital signs will include systolic and diastolic blood pressure

(mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at screening and at the initial visits of Stages 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.15 Electrocardiograms

A 12-lead ECG will be performed during screening, at baseline, Week 4, and at the final visit during Stage 2, and at the first visit (last visit for Stage 2) and at Months 2, 6, 12, 18, and 24 or early termination during Stage 3. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.16 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, and Table 6-3) for details and scheduling.

6.2.16.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2 and at the end of teduglutide exposure in Stage 3. A colonoscopy is required at the beginning of the study, at the end of the main treatment period and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.16.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures – Stage 3, Table 6-3.

Subjects who drop out of the study prior to the final visit should have all end-of-study procedures done.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X[a]	X					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V.		X	X	X	X	X	X[c]
Adverse events		X	X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs		X	X	X	X	X	X
Height		X					
Body weight and BMI		X	X	X	X	X	X[h]
12-lead ECG		X					
Safety laboratory tests		X	X	X	X	X	X
Urine pregnancy test		X					
Interim safety evaluation		[X][i]	[X][i]	[X][i]	[X][i]	[X][i]	
Diary	X[a]	X	X	X	X	X	X
Review 48-hour oral fluid intake[j] (Diary)		X	X	X	X	X	X
Review 48-hour urine output[j] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Optimization assessment[k]		X	X	X	X	X	

BMI = body mass index; ECG = electrocardiogram; GI = gastrointestinal; ICF = Informed Consent Form; PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

Note: One repeat of the optimization/stabilization periods combined is permitted.

[a] The ICF is to be distributed to the subject for review. Once the ICF has been signed by the subject, the diary should be given to the subject in order to record the 48-hour intake/output measurements. No study-related procedures are to be performed unless the ICF has been signed.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for subjects with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in subjects with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be assessed **5 to 7 days** after any scheduled visit **only if a PN/I.V. change** was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[k] The optimization assessment should be made by reviewing the 48-hour oral fluid intake and urine output from the Diary and assessing whether the subject meets the optimization criteria as described in the protocol.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment[c]	X								
Physical examination[d]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V.	X[e]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonoscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[f]		X	X	X	X	X	X	X
Height	X								
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Antibodies to teduglutide and *E. coli* protein	X					X			X
PK sampling	X[j]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation			[X][g, h]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	
48-hour oral fluid intake[i] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[i] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[k]	X	X	X	X	X	X	X	X	X
Compliance[l]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous (volume); V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] Subjects with active Crohn's disease are excluded from the study participation, therefore endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease.

[d] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[e] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[f] This is the second of 2 body weight measurements that will be used to determine drug volume.

[g] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[h] At the Visit 4/Week 2 interim safety visit, laboratory evaluations and 48-hour I/O are not required. These will be assessed only if the PN/I.V. adjustment was tolerated.

[i] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[j] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

[k] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will then self-inject the study drug at home.

[l] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13[b]	Mo 2/14	Mo 3/15[b]	Mo 4/16	Mo 5/17[b]	Mo 6/18	Mo 7/19[b]	Mo 8/20	Mo 9/21[b]	Mo 10/22	Mo 11/23[b]	Mo 12	Final (Mo 24) (or early termination)
Visit Number:	**V1**	**V2/ 14**	**V3/ 15**	**V4/ 16**	**V5/ 17**	**V6/ 18**	**V7/ 19**	**V8/ 20**	**V9/ 21**	**V10/ 22**	**V11/ 23**	**V12/ 24**	**V13**	**V25**
Visit Window (days)		**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Eligibility, Informed consent	X													
Medical history, demographics	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight and BMI	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[g]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Antibodies to teduglutide and *E. coli* protein	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	
Interim safety visit	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]	[X][d]
Diary[e]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[f] (Diary)	X		X		X		X		X		X		X	X
48-hour urine output[f] (Diary)	X		X		X		X		X		X		X	X

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13[b]	Mo 2/14	Mo 3/15[b]	Mo 4/16	Mo 5/17[b]	Mo 6/18	Mo 7/19[b]	Mo 8/20	Mo 9/21[b]	Mo 10/22	Mo 11/23[b]	Mo 12	Final (Mo 24) (or early termination)
Visit Number:	**V1**	**V2/14**	**V3/15**	**V4/16**	**V5/17**	**V6/18**	**V7/19**	**V8/20**	**V9/21**	**V10/22**	**V11/23**	**V12/24**	**V13**	**V25**
Visit Window (days)		**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Teduglutide dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	
Compliance[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X]=Possible interim safety evaluation time point (Refer to footnote "d".); BMI=body mass index; ECG=electrocardiogram; L=liter; Mo=month; PN/I.V.=parenteral nutrition/intravenous (support); V=visit

Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 1 visit. Interim (standard of care) visits may be utilized to assess subjects' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and final visit; a brief examination will be performed at all other study visits.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily.

[g] An ECG will be taken at Visit 3, but not at Visit 15.

[h] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

Data collected during the study will be recorded in the subject's CRF by the investigational site staff. The staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the CRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The PI or designee will review all CRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the CRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. Paper copies non-CRF data will be signed and dated by the investigator and filed.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

All data collected in this study will be entered into an appropriate pre-formatted database and submitted for statistical evaluation. The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the clinical database. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical according to the clinical study protocol, general guidelines, and data management plan. Once the

sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit will be performed by the sponsor's Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by the sponsor or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical

according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the upper limit of the 95% CI of the mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)

- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stage 3

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects) for each treatment group. Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point for each treatment group.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies for each treatment group.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis may also be performed as secondary/sensitivity analysis. Applicable analysis populations will be defined in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its

amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6th revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the sponsor has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator. The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be

informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor’s discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior

review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1: PN/I.V. OPTIMIZATION

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.

2. **Interim Safety Evaluations:** If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

3. Maintain the PN/I.V. level until the next scheduled optimization visit.

4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated by targeted urine output of 1.0 to 2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the sponsor's Medical Monitor.

5. **PN/I.V. Stabilization:** Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2: PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD – STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the sponsor’s Medical Monitor.

Table A2-1: PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. – parenteral nutrition/intravenous (volume)

Table A2-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
*AND consistent with subject's previous levels prior to study entry.
Note: In combination with Table A2-1, any one of the above criteria determines dehydration.
Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. **DOSING WEEKS 2, 4, 8, 12, 16, and 20:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected to evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes:** Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations:** If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration.

At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2-3: Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume)
[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition. During the remainder of the study, subjects may undergo 1 additional attempt to reduce volume by at least 10%.

   d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3: PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **OPTIMIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the sponsor's Medical Monitor.

Table A3-1: PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of optimized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume)

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.

3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits. Depending on the wellbeing of the subject it is at the discretion of the investigator to abstain from the laboratory safety samples.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2: Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
* AND consistent with subject's previous levels prior to study entry.
Note: In combination with Table A3-1, any one of the above criteria determines dehydration.
Note: If weight gain of ≥1.5 kg, request physician review.

APPENDIX 4:

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

_____

Principal Investigator (Print Name)

_____ _____

Principal Investigator (Signature) Date (DD MMM YYYY)

Memo

To: TED-C14-004 Trial Master File (TMF), TED-C14-004 Study Sites
From: [redacted]
Date: Wednesday, 6 January 2016
Subject: Protocol Administrative Change Memorandum

Protocol Title: A 3 Stage Open-label, Multicenter Study Including Long term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN dependent Short Bowel Syndrome

Protocol Version: Protocol v5.0, Amendment 3, Administrative Change #1

The following Administrative Change #1 was made to Protocol TED-C14-004, Version 5.0 and Version date 17 November 2015.

These changes are considered administrative in nature. They do not compromise the scope, design, or integrity of the study, and they do not compromise subject safety in any way.

The following administrative changes have been identified:

1. **Effective 17 December 2015, [redacted] is the [redacted] of EPS Associate Co., Ltd. and the In-Country Clinical Caretaker for Protocol TED-C14-004.**

2. The fax contact information for EPS Associate Co., Ltd. given on the title page is incorrect. **The correct fax number is [redacted].**

3. **The sponsor wishes to clarify that the number of study kits dispensed at a study visit may be adjusted and study kits may be dispensed between study visits as an option at the discretion of the Investigator and patient.**

Copies of this memo shall be distributed to the Principal Investigators of the study and to the Shire Study Team.

I have reviewed the above Memo and am in agreement with the specified administrative change.

[redacted] MD [redacted] Date

TED-C14-004 Project Physician

Memo

Shire

To: TED-C14-004 Study Sites
From: [redacted]
Date: Thursday, 23 June 2016
Subject: Protocol Administrative Clarification Memorandum

Protocol Title: A 3 Stage Open-label, Multicenter Study Including Long term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN dependent Short Bowel Syndrome

Protocol Version: Protocol v5.0, Amendment 3, Administrative Letter #2

The following Administrative Letter #2 was made to Protocol TED-C14-004, Version 5.0 and Version date 17 November 2015. These clarifications do not compromise the scope, design, or integrity of the study, and they do not compromise subject safety in any way.

The following administrative clarifications have been identified:

1. Antibody testing to teduglutide: Section 6.2.4 of the protocol implies that subjects with a positive antibody test at the end of Stage 2 are to have additional antibody testing completed every 2 months during Stage 3. However, the Schedule of Evaluations and Procedures (Table 6-3) of the protocol only requires this testing at months 6, 12, 18, and 24 or early termination during Stage 3. This letter serves to clarify that antibody testing will occur at months 6, 12, 18, and 24 or early termination during Stage 3, as outline in Table 6-3 of the protocol.

2. This letter serves to clarify that any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will be collected on the study case report forms.

Copies of this memo shall be distributed to the Principal Investigators of the study and should be forwarded to site Ethics Committees as necessary.

I have reviewed the above Memo and am in agreement with the specified administrative clarifications.

[redacted] _____ [redacted]

[redacted] MD Date

[redacted]
TED-C14-004 Project Physician

cc: TED-C14-004 Trial Master File (TMF)

Memo

To: TED-C14-004 Study Sites
From: [redacted]
Date: Thursday, 23 June 2016
Subject: Protocol Administrative Clarification Memorandum

Protocol Title: A 3 Stage Open-label, Multicenter Study Including Long term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN dependent Short Bowel Syndrome

Protocol Version: Protocol v5.0, Amendment 3, Administrative Letter #3

The following Administrative Letter #3 was made to Protocol TED-C14-004, Version 5.0 and Version date 17 November 2015. This clarification does not compromise the scope, design, or integrity of the study, and it does not compromise subject safety in any way.

The following administrative clarification has been identified:

1. Frequency of antibody testing to teduglutide: Blood samples are currently screened for the presence of antibodies to teduglutide as soon as they are collected according to the Schedule of Evaluations and Procedures in the protocol. For the remainder of the study, these samples will be stored and then analysed together periodically to streamline the testing procedure. Testing will occur on at least 2 more occasions (in time to provide data for interim analysis report #2 and again at the end of the study). There is no evidence to date to indicate that the presence of anti-drug antibodies impacts efficacy or safety of teduglutide, so this change will not compromise subject safety. However, if a Principal Investigator suspects that a subject is experiencing an antibody-related adverse event, relevant samples will be tested for the presence of anti-drug antibodies upon request.

Copies of this memo shall be distributed to the Principal Investigators of the study and should be forwarded to site Ethics Committees as necessary.

I have reviewed the above Memo and am in agreement with the specified administrative clarifications.

[redacted] MD

[redacted] Date

TED-C14-004 Project Physician

cc: TED-C14-004 Trial Master File (TMF)

Memo

To: TED-C14-004 Study Sites
From: [redacted]
Date: 02 August 2016
Subject: Protocol Administrative Clarification Memorandum

Protocol Title: A 3 Stage Open-label, Multicenter Study Including Long term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN dependent Short Bowel Syndrome

Protocol Version: Protocol v5.0, Amendment 3, Administrative Letter #4

The following Administrative Letter #4 was made to Protocol TED-C14-004, Version 5.0, dated 17 November 2015. This clarification does not compromise the scope, design, or integrity of the study, and does not compromise subject safety in any way.

The following administrative change is to be made:

1. [redacted] MD, PhD., will replace [redacted] MD as the Medical Monitor for the TED-C14-004 study as of 05 August 2016. Dr. [redacted] contact information is as follows:
   Office: [redacted]
   Mobile: [redacted]
   Email: [redacted]

   The protocol will be updated with this change during the next protocol amendment.

Copies of this memo shall be distributed to the Principal Investigators of the study and should be forwarded to site Ethics Committees as necessary.

I have reviewed the above Memo and am in agreement with the specified administrative clarifications.

[redacted]
MD, PhD
[redacted]
TED-C14-004 Project Physician

[redacted]
Date

cc: TED-C14-004 Trial Master File (TMF)

A 4-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Clinical Study Protocol TED-C14-004

Version 6.0

Phase 3

Sponsor:
NPS Pharmaceuticals, Inc.*

550 Hills Drive, 3rd Floor

Bedminster, NJ 07921

USA

(*NPS was acquired by Shire, Inc. on 21 February 2015)

Medical Monitor (Medical Expert of the Sponsor):
[redacted], MD PhD
[redacted] Global Clinical Development

In-Country Clinical Caretaker:
[redacted]
[redacted]
EPS Associate Co., Ltd.
2-23 Shimomiyabicho, Shinjuku-ku,
Tokyo 162-0822, Japan

TEL: [redacted] FAX: [redacted]

Protocol v1.0:05 August 2014
Protocol v2.0, Amendment 1:20 August 2014 (administrative amendment)
Protocol v3.0, Amendment 1 (corrected):15 September 2014
Protocol v4.0, Amendment 2:03 March 2015
Protocol v5.0, Amendment 3:17 November 2015
Protocol v6.0, Amendment 4:03 April 2017

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must mail the sponsor's Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the sponsor's Global Drug Safety Department. Applicable e-mail address can be found on the form (sent under separate cover) and below. A copy of this form must also be sent to the sponsor's Medical Monitor by e-mail using the details below.

Shire Global Drug Safety
E-mail: [redacted]

[redacted] **MD PhD, Medical Monitor**
Office: [redacted]
Mobile: [redacted]
E-mail: [redacted]

SUMMARY

Protocol TED-C14-004

Title of Study: A 4-Stage, Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

Protocol No: TED-C14-004

Phase of development: 3

Objectives: The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS) over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

Methodology: This will be an open-label, multicenter, 4-stage study. All subjects will receive teduglutide 0.05 mg/kg/day. Stage 1 will include a screening visit; a maximum 8-week parenteral nutrition/intravenous fluids (PN/I.V.) support optimization period (if required); and a stabilization period in which stable administration of PN/I.V. support, defined as a targeted urine output of 1.0 to 2.0 L/day while the subject is kept adequately hydrated and nourished, is demonstrated for a minimum of 4 weeks up to a maximum of 8 weeks. If a subject fails to remain stable for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Visit 1.1. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be dosed. Stage 2 will be a dosing period of 24 weeks, during which subjects will self-administer the study drug at home.

Stages 3 and 4 constitute the long-term extension portion of the study. In Stage 3, which will begin immediately following Stage 2, subjects will continue to receive treatment with teduglutide 0.05 mg/kg/day for up to 24 months. In Stage 4, which will begin immediately following Stage 3, subjects will continue treatment with teduglutide 0.05 mg/kg/day in Study TED-C14-004 until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

Any subject who achieves complete independence from PN/I.V. support at any time during the Stages 2, 3 or 4 treatment periods will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

Number of subjects planned: At least 5 subjects may be enrolled.

Diagnosis and main criteria for inclusion: Men and women outpatients, aged 16 years and older at the time of signing the Informed Consent Form (ICF) who meet the following criteria:

- Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of the ICF
- In clinical remission from Crohn's disease for at least 12 weeks prior to dosing

- PN/I.V. support required at least 3 times per week during the week prior to screening and during the 2 weeks prior to baseline to meet their caloric, fluid or electrolyte needs
- Stable PN/I.V. support for at least 4 consecutive weeks immediately prior to the start of treatment with teduglutide, based upon the opinion of the investigator and approval by the Sponsor's Medical Monitor; stability is defined as:
    - Actual PN/I.V. usage matches prescribed PN/I.V.
    - Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time the subject is optimized and enters stabilization.
    - Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.
- Adequate hepatic function at the time of stabilization:
    - Total bilirubin < 2 times upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) < 5 times ULN
    - Alanine aminotransferase (ALT) < 5 times ULN
- Adequate renal function at the time of stabilization:
    - Serum creatinine < 2 times ULN
    - Creatinine clearance ≥ 50 mL/minute (only in subjects with a known history of creatinine clearance < 50 mL/min)
- Adequate pancreatic function at the time of stabilization:
    - Serum amylase < 2 times ULN
    - Serum lipase < 2 times ULN
- No unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
- No radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome
- No evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening
- No current diagnosis of cancer or history of any cancer except basal cell carcinoma within 5 years
- No evidence of untreated intestinal obstruction or clinically significant active stenosis

Test product, dose and mode of administration: Teduglutide for subcutaneous (SC) injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection and used within 5 minutes of reconstitution.

A daily dose of teduglutide 0.05 mg/kg will be used in this study. The dose calculation will be based on an average of the 2 measurements of body weight at the stabilization and baseline visits. This calculated dose will be used for the duration of the study, however, it may be adjusted for change in a subject's weight when entering Stage 4 (Visit 26).

Teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or either thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. The first SC injection should be administered under the supervision of the investigator or designee.

Reference therapy, dose and mode of administration: This is an open-label study.

Duration of treatment:

In Stage 1, subjects will undergo screening (taking up to 7 days), a maximum 8-week PN/I.V. support optimization period (if required), and a stabilization period that demonstrates stable administration of PN/I.V. support for a minimum of 4 weeks up to a maximum of 8 weeks (total maximum 16 weeks for optimization/stabilization periods). Subjects who fail optimization or stabilization may return to the beginning of the optimization period once (taking up to an additional 16 weeks). Therefore the total possible duration of Stage 1 is up to 33 weeks.

Following Stage 1, subjects will self-administer study treatment at home for 24 weeks in the main treatment period (Stage 2).

After the initial 24-week treatment period (Stage 2), subjects will continue teduglutide treatment in the initial extension treatment period for up to an additional 24 months (Stage 3). The extension treatment period will continue in Stage 4 where subjects will receive treatment with teduglutide in Study TED-C14-004 until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

Criteria for Evaluation

Efficacy and pharmacodynamics – Stage 2: The efficacy variables are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

Efficacy and Pharmacodynamics – Stages 3 and 4: Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

Pharmacokinetics – Stage 2 only: Single-dose PK will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

Safety: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide and to *Escherichia coli* protein (ECP), and changes in 48-hour urine output, body weight and body mass index (BMI) will be evaluated. An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not done in the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (at Stages 3 and 4). For all subjects with a history of Crohn's disease, an upper gastrointestinal (GI) contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

Statistical methods: No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval. For categorical variables, n (%) will be summarized. Individual data will be listed.

PK parameter estimates will be calculated using a non-compartmental analysis.

Interim Analysis: An interim analysis of study data will be done at the completion of the 24-week Stage 2 study period and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

SIGNATURE PAGE

Protocol TED-C14-004

Reviewed and Approved:

[redacted], **MD PhD**
[redacted]
Global Clinical Development

[redacted]
Signature

[redacted]
Date
(DD MMM YYYY)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase, equivalent to SGPT
ALX-0600	Teduglutide
AST	Aspartate aminotransferase, equivalent to SGOT
ATC	Anatomic Therapeutic Class
AUC	Area under the plasma concentration-time curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve from zero to infinity
$AUC_{0–t}$	AUC from zero to the last measurable concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic case report form
ECP	*Escherichia coli* protein
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Glucagon-like peptide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
I/O	Oral fluid intake and urine output
IRB	Institutional Review Board
ITT	Intent-to-treat
I.V.	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator

PK	Pharmacokinetics
PN	Parenteral Nutrition: includes fluids and electrolytes, and may include energy and micronutrients
PN/I.V.	Parenteral Nutrition/Intravenous Fluids
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SUSAR	Suspected, unexpected, serious, adverse reaction
$t_{1/2}$	Terminal-phase half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Compound

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide (GLP)-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines. The European Commission granted a centralised marketing authorization valid throughout the European Union for teduglutide (Revestive®) on 30 August 2012 and a New Drug Application for teduglutide (Gattex®) was approved by the US Food and Drug Administration on 21 December 2012 for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support.

Nonclinical Studies

Cardiovascular and respiratory safety pharmacology studies with teduglutide were conducted in beagle dogs and no treatment-related effects were observed that were attributed to teduglutide. No effect of teduglutide was noted on the *in vitro* hERG channel or canine cardiac Purkinje fibers. In addition no central nervous system effects were observed in rodents in which teduglutide was administered at doses well above the targeted clinical therapeutic dose.

Pivotal repeat-dose toxicity studies were conducted in mice and monkeys; genotoxicity was studied in mice; carcinogenicity was investigated in rats and mice; reproductive and developmental toxicity were investigated in rats and rabbits; and toxicity in juvenile animals was investigated in minipigs.

The pattern of toxicity after repeated dosing has been consistent among the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an exaggerated or extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, up to 104 weeks in rats and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in organs that are most likely affected by retrograde diffusion (ie, intrahepatic and extrahepatic bile ducts in mouse, rat and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey). The intestinal changes in the toxicity studies occurred in a non-dose-related manner (indicating that the plateau phase of the dose-response curve had been reached) and were reported at all teduglutide doses. For the non-target organs, the findings are considered to represent an extension or exaggeration

of the pharmacology of the drug. The intestinal changes largely resolved during a recovery period of several weeks.

The effects in the other organs either partially or completely resolved during the recovery period. Inflammation at the site of injection was noted in most species, but was most pronounced in monkeys.

Teduglutide was negative in standard *in vitro* and *in vivo* genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumors in the bile duct and jejunum was observed with a clearly defined No-Observed-Effect-Level. These tumors were consistent with the drug's activity as a growth factor for the intestine. No treatment- related malignant tumors were observed following treatment with teduglutide.

The carcinogenic potential of teduglutide was assessed in two 2-year carcinogenicity studies in which teduglutide was administered subcutaneously (SC) in rats and mice. In Wistar Han rats at SC doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In Crl:CD1(ICR) mice at SC doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gallbladder; it also caused adenocarcinomas in the jejunum in male mice at the highest dose.

Even at high doses, teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and postnatal development in rats. The same pharmacological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the pediatric population.

Teduglutide is considered non-immunogenic in mice, rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide.

Toxicokinetic analyses revealed that teduglutide was rapidly absorbed following SC injection. Maximum concentration (C_{max}) and area under the curve (AUC) values generally increased in a dose proportional manner with no evidence of accumulation. Male mice and rats tended to exhibit higher exposures than females, but this effect was not pronounced and was not observed in minipigs or monkeys.

Clinical Studies

Results of the pivotal study filed for the United States (US) New Drug Application, CL0600-020, showed that teduglutide at a dose of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing parenteral nutrition/intravenous fluids (PN/I.V.) volume in adult subjects with SBS.

In this study the responder rate was 62.8% in the teduglutide 0.05 mg/kg/day group with subjects achieving a mean reduction from baseline in PN/I.V. volume of 4.4 L/week at Week 24.

In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. The most significant reductions were for those subjects who received 24 weeks of teduglutide 0.05 mg/kg/day in Study CL0600-020 and continued treatment in Study CL0600-021 for another 24 months. In this cohort, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. It is encouraging that further efficacy was also observed for subjects who initiated treatment in Study CL0600-021 (ie, those who received placebo in Study CL0600-020). After only 6 months of treatment, 37.1% these subjects had at least a 20% reduction in weekly PN/I.V. volume, which increased to 55.2% by Month 24. Two subjects completely weaned off of their PN/I.V. support.

Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

The results of this study continue to support the efficacy of long-term treatment with teduglutide in PN/I.V.-dependent SBS subjects.

1.2 Rationale for the Clinical Study

Teduglutide 0.05 mg/kg/day has demonstrated a favorable benefit-risk profile in clinical studies and is already marketed in the European Union (EU) and the US. The clinical profile and issues related to SBS and PN/I.V. in Japan are similar to those in the EU and US. Therefore, there is an unmet medical need for Japanese patients with PN-dependent SBS. This study is designed to provide evidence of safety and efficacy of teduglutide in a Japanese SBS patient population.

1.3 Rationale for Study Design

The design of this study is based on the previously conducted multicenter, multinational pivotal study. The dose, treatment duration and design of the current study are supported by the results of previous studies. Pivotal study CL0600-020 showed that teduglutide at a dosage of 0.05 mg/kg/day for up to 24 weeks was superior to placebo in reducing PN/I.V. volume in adult subjects with SBS. In the follow-up long-term extension study CL0600-021, there continued to be evidence of increased efficacy of teduglutide over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction, gaining additional days off per week, and achieving complete weaning of parenteral support. Among the subjects who received 24 weeks of teduglutide treatment in Study CL0600-020 and who continued treatment in Study CL0600-021 for another 24 months, 10 subjects completely weaned off of PN/I.V. support and 18/30 (60.0%) had a reduction in their PN/I.V. requirement of at least 3 days. Overall, reductions ranged from 13 PN-dependent subjects achieving complete weaning to 25/65 (38.5%) subjects who

demonstrated a reduction of ≥ 3 days/week in their parenteral support by the end of study at Month 24. In addition, 21/22 (95.5%) of teduglutide-treated subjects who responded in the previous study maintained their response after an additional 24 months of teduglutide treatment, demonstrating durability of effect.

2 OBJECTIVES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics (PK) of teduglutide in Japanese subjects with PN-dependent SBS over a 24-week period followed by a long-term extension to evaluate long-term safety and efficacy.

2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2 Efficacy and Pharmacodynamic Endpoints – Stages 3 and 4

For Stages 3 and 4, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.3 Pharmacokinetic Endpoints – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Baseline/Day 0). Samples for PK analysis will be collected and recorded pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

The following parameters will be derived:

- Area under the plasma concentration–time curve (AUC) from zero to infinity (AUC_{0-inf})
- AUC from zero to the last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Terminal-phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)

- Apparent volume of distribution (V/F)

2.4 Safety Objectives

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period (Stage 2) and at the end of the extension treatment period (at Stages 3 and 4). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

3 STUDY DESIGN

This will be an open-label, multicenter, 4-stage study, consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stages 3 and 4).

3.1 Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Appendix 1 provides details of the optimization procedure. Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least

5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

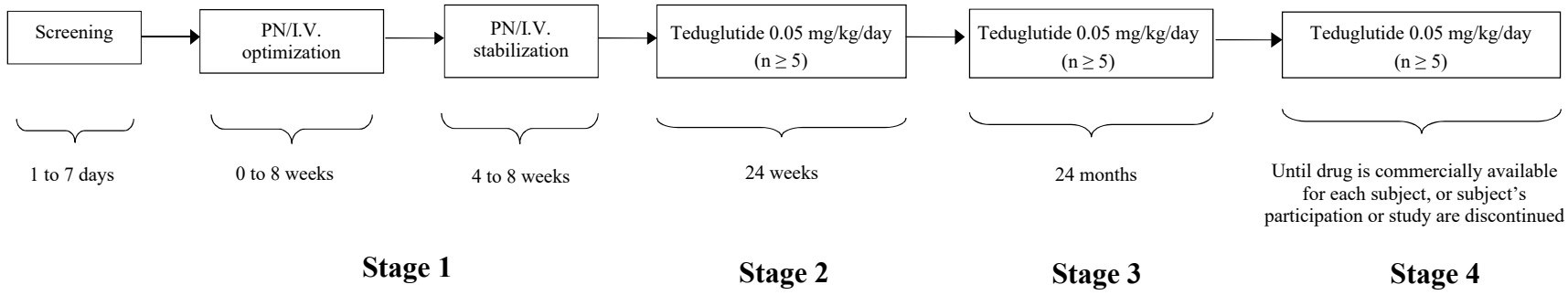
3.2 Extension Treatment Period (Stages 3 and 4)

Stages 3 and 4 constitute the long-term extension portion of the study. Stage 3, which will begin immediately following Stage 2, will include subjects who complete the main treatment period and who are willing to continue with treatment teduglutide 0.05 mg/kg/day SC for up to an additional 24 months. In Stage 4, which will begin immediately following Stage 3, subjects will continue treatment with teduglutide 0.05 mg/kg/day SC in Study TED-C14-004 until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

Any subject who achieves complete independence from PN/I.V. support at any time during the Stages 2, 3 or 4 treatment periods will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

A schematic representation of the study design is presented in Figure 3-1.

Figure 3-1 Study Diagram



Schedules of evaluations for Stage 1, 2, 3 and 4 can be found in Table 6-1, Table 6-2, Table 6-3, and Table 6-4, respectively.

Procedures to adjust or reduce PN/I.V. volume during the optimization can be found in Appendix 1 and during treatment periods in Appendix 2 and Appendix 3, and should be followed carefully throughout the study.

4 SUBJECT SELECTION AND PARTICIPATION

4.1 Number of Subjects

At least 5 subjects with PN/I.V.-dependent SBS will be enrolled.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1. Signed and dated Informed Consent Form (ICF) before any study-related procedures are performed

2. Men and women, 16 years of age or older at the time of signing the ICF

3. Subjects with SBS as a result of major intestinal resection (eg, due to injury, volvulus, vascular disease, cancer, Crohn's disease) that resulted in at least 12 continuous months of PN/I.V. dependency prior to signature of ICF

4. For subjects with a history of Crohn's disease, the subject should be in clinical remission for at least 12 weeks prior to dosing as demonstrated by clinical assessment, which may include procedure-based evidence of remission.

5. PN/I.V. requirement of at least 3 times per week during the week before screening and during the 2 weeks prior to baseline to meet caloric, fluid or electrolyte needs

6. Stable PN/I.V. requirement for at least 4 consecutive weeks immediately prior to the start of teduglutide treatment, based upon the opinion of the investigator and approval by the sponsor's Medical Monitor or designee; stability is defined as:
    a. Actual PN/I.V. usage matches prescribed PN/I.V.
    b. Baseline (Visit 2) 48-hour oral fluid intake and urine output (I/O) volumes fall within ± 25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization
    c. Urine output volume should NOT fall below 2 L and should not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods.

4.2.1 Inclusion in Stage 3

Subjects who meet the following criterion will be enrolled in Stage 3 and Stage 4 of this study:

1. Completion of 24 weeks of dosing and still meeting the criteria for enrollment

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Participation in a clinical study using an experimental drug within 30 days or an experimental antibody treatment within 3 months prior to signing the ICF, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide

2. Previous use of native GLP-2 or human growth hormone within 6 months prior to screening

3. Previous use of intravenous glutamine, octreotide, GLP-1 analog, or dipeptidyl peptidase-IV inhibitors within 30 days prior to screening

4. Previous use of teduglutide

5. Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months

6. Subjects with active Crohn's disease or subjects who require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that had been introduced or changed during the 6 months prior to screening

7. Subjects with inflammatory bowel disease who require chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months

8. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)

9. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome

10. Evidence of clinically significant obstruction on upper GI series with small bowel follow-through done within 6 months prior to screening

11. Major GI surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)

12. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair

13. Currently diagnosed with cancer or a history of any cancer except basal cell carcinoma within 5 years

14. Active clinically significant pancreatic or biliary disease

15. More than 4 SBS-related or PN-related hospital admissions (eg, catheter sepsis, bowel obstruction, severe water-electrolyte disturbances) within 12 months prior to screening visit

16. Hospital admission, other than scheduled, within 30 days prior to screening

17. Signs of severe hepatic impairment at time of stabilization:
    a. Total bilirubin level ≥ 2 times the upper limit of normal (ULN); for subjects with Gilbert's disease, direct (conjugated) bilirubin level ≥ 2 times ULN
    b. Aspartate aminotransferase (AST) ≥ 5 times ULN
    c. Alanine aminotransferase (ALT) ≥ 5 times ULN

18. Signs of disturbed renal function at time of stabilization:
    a. Serum creatinine ≥ 2 times ULN
    b. Creatinine clearance < 50 mL/minute*

    *Only applies to subjects with a known history of creatinine clearance (CrCl) < 50 mL/min who then will be required to have a CrCl ≥ 50 mL in order to participate in the study. If a CrCl cannot be measured, an estimated glomerular filtration rate (eGFR) may be calculated.

19. Clinical signs of abnormal pancreatic condition, with abnormal laboratory results at time of stabilization including:
    a. Serum amylase level ≥ 2 times ULN
    b. Serum lipase level ≥ 2 times ULN

20. Pregnant or lactating women

21. Female subjects who are not surgically sterile or postmenopausal (defined as 55 years or older and/or at least 2 years had elapsed since her last menses) or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period

22. Not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements

23. Evidence of untreated intestinal obstruction or clinically significant active stenosis

24. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results

25. Presence of any of the excluded disease states described in Table 4-1

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Active celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease that requires chronic systemic immunosuppressant therapy that was introduced or changed during the last 3 months
	Crohn's disease or other diseases that require biological therapy (eg, anti-tumor necrosis factor or natalizumab) that was introduced or changed in the last 6 months
	Untreated known pre-malignant or malignant change in upper or lower GI biopsy or polypectomy
	Known, untreated, polyposis conditions (ie, familial adenomatous polyposis, Peutz-Jeghers syndrome, Turcot syndrome, Juvenile polyposis syndrome, Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, Gardner's syndrome, Cronkhite-Canada syndrome)
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic active pancreatitis or active cholecystitis
Immune	Compromised immune system (eg, acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness

Table 4-1 Excluded Diseases and Illnesses

Body system or disease type	Known conditions excluded
General	Significant active, uncontrolled, untreated systemic diseases (eg, cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

4.4 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to further treatment. Discontinued subjects will not be replaced.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. If the reason is not disclosed, every effort must be made up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section 6.2.1.2. As far as possible, all examinations scheduled for the early termination evaluations must be performed on all subjects who participate, but do not complete the study according to the protocol.

4.4.1 Events Necessitating Withdrawal from Study

The sponsor or designee should be consulted prior to premature withdrawal of a subject. The occurrence of any of the following events may necessitate premature withdrawal of a subject from the study:

- Development of any of the following Inclusion/Exclusion criteria that would interfere with analysis of the study results (ie, compromise PN/I.V.):
    - Significant active, uncontrolled diseases (eg, cardiovascular, renal, cancer) that would put the subject at any undue risk or prevent completion of the study
    - Major surgical interventions (eg, abdominal, vascular)
    - Crohn's disease flare up
    - Use of any excluded medication
    - Pregnant and lactating women
- Occurrence of a serious adverse event (SAE) thought to be related to study drug and not alleviated by symptomatic treatment
- Unwillingness to continue in the clinical study
- Death of the subject
- Investigator/Sponsor decision (ie, subject non-compliance with study procedures)

- Significant AE or medical decision that precludes the subject from adhering to study requirements

4.4.2 Re-screening of Subjects

In the event that a subject withdraws from the study in Stage 1, that subject may be re-screened upon the approval of the sponsor. A new subject number will be assigned.

Subjects whose urine output cannot be stabilized during the stabilization period after 1 repeated effort may not be rescreened.

5 TREATMENTS AND TREATMENT PLAN

After signing the ICF, the subject will enter Stage 1 of the study, which includes screening, optimization and stabilization. The purpose of this stage is to ensure that all subjects are receiving and tolerating a stable minimal (optimized) level of PN/I.V. volume before treatment with teduglutide. If needed, the subject will enter an 8-week maximum optimization period, during which the PN/I.V. volume will be adjusted stepwise in targeted increments of 10% or more of the previous visit's volume (Appendix 1). Once the PN/I.V. volume is optimized, the subject will enter a minimum 4-week to 8-week stabilization period.

The aim of the study is to evaluate the efficacy of teduglutide in allowing reductions of PN/I.V. volume to less than the stabilized PN/I.V. level. After completion of the PN/I.V. stabilization period, subjects will enter Stage 2 of the study and receive teduglutide for a 24-week dosing period. The algorithm for the stepwise reduction of PN/I.V. during the Stage 2 dosing period is in Appendix 2.

Stages 3 and 4 constitute the long-term extension portion of the study. Stage 3 will begin immediately following Stage 2 and Stage 4 immediately following Stage 3. In Stages 3 and 4, subjects can continue teduglutide treatment if deemed appropriate by the investigator. During the extension, the PN/I.V. dosage will be adjusted as described in Appendix 3. Subjects will continue to receive teduglutide 0.05 mg/kg/day in Stage 3 for up to 24 months then in Stage 4 until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

Any subject who achieves complete independence from PN/I.V. support at any time during Stages 2, 3 or 4 will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.1 Treatments Administered

Teduglutide 0.05 mg/kg/day will be administered daily at home by the subjects, who will self-administer the study drug by SC injection into either thigh or arm or one of the 4 quadrants of the abdomen (in subjects without a stoma). For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

5.1.1 Identification of Investigational Product

Teduglutide for SC injection is provided as a lyophilized powder that must be reconstituted using 0.5 mL sterile water for injection, and used within 5 minutes of reconstitution. The Injection Instruction Leaflets will be provided separately. Each 3.0 mL vial contains 5 mg of teduglutide.

Active ingredient:teduglutide

Added ingredients:L-histidine, mannitol, monobasic and dibasic sodium phosphate

Route of administration:SC injection

Dose:0.05 mg/kg/day

5.1.2 Packaging and Labeling

Study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. The study drug kit labeling will include the protocol number, the investigational drug warning, storage conditions, expiry date, drug name or drug code, lot number, sponsor name and country and In-Country Clinical Caretaker name and address. All medication supplied to be used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice. Ancillary supply kits containing the following will also be provided with the study drug at each visit:

- Pre-filled syringes of sterile water for injection
- Needles to affix to sterile water for injection syringes for reconstitution; or vial adaptors for reconstitution and withdrawal of the reconstituted study drug into the dosing syringe
- Syringes and needles for injection (dosing)
- Alcohol swabs

5.1.3 Storage, Accountability, and Stability

Study drug will not be dispatched to the center until the sponsor or designee has received all required documents from the study center in accordance with applicable regulatory requirements and relevant standard operating procedures.

The investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records. Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug must be stored refrigerated at a temperature between 2 and 8^{o}C (36 to 46^{o}F) until dispensed. Once dispensed to a subject, the study drug and the sterile water diluent should be kept at 15 to 25^{o} C (59 to 77^{o}F). If there are concerns that this temperature cannot be maintained, the study drug may be refrigerated. Therefore, the overall acceptable storage temperature range is 2 to 25^{o}C (36 to 77^{o}F).

Study drug kits will be dispensed to subjects at each of the study visits. Each study drug kit is sufficient for a treatment period of 1 week and enough kits are to be supplied to cover the period until the next planned study visit. The number of study kits dispensed at a study visit may be adjusted and study kits may be dispensed between study visits as an option at the discretion of the investigator and the subject. Additional study kits will be provided as necessary.

The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded, with an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

All used and unused study drug vials, including the supplies must be returned by the subjects and retained at the center until instructions are received for return and/or destruction of supplies. Further details will be provided in the study reference manual.

5.2 Dose Regimen

The volume of reconstituted study drug is to be administered at a fixed dose of 0.05 mg/kg. The dose will be calculated as an average of the 2 measurements of body weight at the stabilization and baseline visits. The dose of study drug administered at baseline should be maintained throughout the study period without adjustments for changes in a subject's weight except at Visit 26 when entering Stage 4 of the study.

5.2.1 Selection of Doses in Study

The dose of teduglutide selected for this study is based on the efficacy and safety results of up to 2 ½ years of treatment in prior studies, as discussed in Section 1.3. Due to the favorable risk/benefit profile, the teduglutide dose of 0.05 mg/kg/day was chosen as the dose for all adult safety and efficacy studies.

5.2.2 Selection and Timing of Dose for Each Subject

The study drug (teduglutide 0.05 mg/kg/day) will be self-administered immediately after reconstitution by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm. Subjects will be trained to self-inject teduglutide on Day 0. The first SC injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Detailed instructions for reconstitution and injection of the study drug can be found in the Injection Instruction Leaflets and the study reference manual. Each day, the injection site should be changed. Subjects with a stoma must avoid using the abdominal quadrant in which the stoma is situated.

The subject should be dosed at approximately the same time each day. If a subject forgets to take drug, that day's dose should be administered as soon as possible, even if this is later in the day or evening. Consecutive doses should be separated by approximately 12 hours.

First dosing with investigational product must be performed after the blood drawn for antibody testing at baseline (Visit 2) in Stage 2. Once the subject has started teduglutide treatment, dosing

must be performed at least 14 hours prior to the blood drawn for antibody testing, which will be performed at: Baseline and Weeks 12 and 24 during Stage 2; Months 6, 12, 18, and 24 (or early termination) during Stage 3; and every other visit (every 6 months) and end-of-study (or early termination) visit during Stage 4.

The investigator is responsible for contacting the sponsor or designee prior to interrupting or modifying the subject's daily study drug dosing regimen, ie, as consideration for tolerability issues.

A single discontinuation period of study drug should not exceed 10 consecutive days. Dosage interruptions of study drug are permissible for a maximum of 21 days total per each 24-week period throughout the study.

Dates of days with missed or incomplete doses are to be reported in the diary.

5.2.3 Subjects Who Achieve PN/I.V. Independence

Any subject who achieves complete independence from PN/I.V. support at any time during the Stages 2, 3 or 4 treatment periods will continue to receive teduglutide treatment. A subject will be considered to have achieved independence from PN/I.V. (completely weaned off PN/I.V.) if the investigator prescribes no PN/I.V. and there is no use of PN/I.V. recorded in the subject diary at the last dosing visit.

If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

5.2.4 Compliance with Dosing Regimens

Subject compliance with study drug dosing will be monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance will be checked at every visit by asking the subjects if they have taken their study drug according to instructions and by performing drug accountability.

Compliance is considered to be achieved if the subject has 80% of the planned doses administered.

5.3 Prior and Concomitant Medications

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins), study drug, and PN/I.V. must be recorded from screening and for the duration of the study in the appropriate sections of the CRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the CRF.

No new medications should be started unless medically necessary and prescribed by the investigator or by another qualified physician involved in the subject's clinical care and who is aware of the subject's study participation.

The mechanism of action of teduglutide may increase absorption of orally administered drugs (eg, motility medication, warfarin, psychotropics, and digoxin), so consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medication dosages should be considered when drugs, including those with a narrow therapeutic range, are given, especially if given at dosages that are higher than usual.

6 STUDY EVALUATIONS AND PROCEDURES

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stages 3 and 4) to evaluate safety and continued efficacy.

6.1 Efficacy Evaluations

Reductions in PN/I.V. volume form the basis for most of the efficacy evaluations. The procedures for the stepwise reduction of PN/I.V. during Stages 2 to 4 of this study are given in Appendix 2 (Stage 2) and Appendix 3 (Stages 3 and 4).

As described in Section 2.1, the efficacy endpoints for Stage 2 are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

In Stages 3 and 4, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension (see Section 2.2).

Single-dose pharmacokinetics will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 only, and pharmacokinetic parameters will be derived as described in Section 2.3.

6.2 Safety Evaluations

Safety will be assessed by evaluations of the following variables:

- Adverse events, including GI symptoms
- 12-lead ECGs
- Vital signs, including changes in body weight and BMI
- Laboratory safety data, including electrolyte balance
- Antibodies to teduglutide and ECP (see Table 6-1, Table 6-2, Table 6-3, and Table 6-4 for timing)
- Changes in urine output (48-hour oral fluid intake/urine output)

- Abdominal ultrasound
- Upper GI contrast series with small bowel follow-through
- Colonoscopy/sigmoidoscopy of remnant colon
- Physical examinations

6.2.1 Adverse Events

During the study, the investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol.

6.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 6.2.1.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE. The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – An accidental or intentional administration of an excessive dose of a product
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

6.2.1.2 Procedures for Reporting Adverse Events

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of the ICF and for the duration of the study. Adverse events that are not resolved at the end of study will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug or until resolution or until the AE is judged by the investigator to have stabilized.

As they occur, new AEs will be recorded sequentially on the AE page of the CRF. The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time (date the site becomes aware of the SAE)
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)

  - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
  - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
  - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required
- Relationship to study drug (not related, related): identify relationship as "related" if a causal relationship between the investigational product and an AE is at least a reasonable possibility (see Section 6.2.2.2 for additional guidance on relationship to study drug)
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2 below.
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, unknown, fatal). An individual AE receives only one outcome.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator (ie, not part of the subject's medical history),
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

6.2.2 Serious Adverse Events

An SAE must be recorded on the SAE Form. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug or the end of the study, whichever is longer, will be captured and must be reported within 24 hours after the investigator is made aware of the event.

6.2.2.1 Serious Adverse Event Definition

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject – in the investigator's opinion – at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- Planned before entry into the clinical study
- Elective treatment of a condition unrelated to the studied indication or its treatment
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

6.2.2.2 Procedures for Reporting Serious Adverse Events

All initial and follow-up SAE reports must be reported by the investigator to the sponsor's Global Drug Safety Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 6.2.1.1) unless they result in an SAE.

The investigator must complete, sign, and date the sponsor's Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and e-mail the form to the sponsor's Global Drug Safety Department. A copy of the sponsor's Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the sponsor's Medical Monitor using the details specified in the emergency contact information section of the protocol.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but an SAE criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an AE, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the SAE form.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the

cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see below). A causality assessment should always be included on the SAE form. The investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the event should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the event, then the event should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol.

As required by ICH guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not in the appendix to the Investigator Brochure (IB) that contains the compound adverse drug reactions; or if the event is of greater frequency, specificity, or severity than is recorded in the

IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study. The investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

The investigator should also comply with the Institutional Review Board (IRB) procedures for reporting any other safety information (eg, autopsy reports).

The sponsor or its designee will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe.

6.2.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting for this study include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the Shire Global Drug Safety Department must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 6.2.2.2 even if the event does not fulfill seriousness criterion.

6.2.4 Pregnancy Reporting

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 3.2.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event

and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

6.2.5 Laboratory Evaluations

Laboratory results can vary depending on whether samples are drawn on an on- or off-PN/I.V. day, so it is important that every effort be made to draw laboratory samples on the same type of infusion day (ie, on- or off-PN/I.V.) throughout the study. Although subjects do not need to be in a fasted state at the time of their clinic visit, they should avoid large meals or large volumes of fluid, including PN/I.V. with lipids, within 3 hours of the clinic visit to permit consistent assessment. If peripheral venous access is not possible, the sample may be drawn from the central line. A home nursing visit may be appropriate to collect samples in some circumstances. The site's clinical laboratory will centrifuge and send the samples to the central lab, SRL Medisearch Inc. to be analyzed. Citrulline, antibody, and PK samples will be handled according to procedures specified in the laboratory manual.

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs if they are not related to the subject's underlying condition or their previous comorbid medical history (unless they are a worsening of the condition). A result outside of the normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (Section 6.2.2) must also be recorded in an SAE Form so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

The following laboratory parameters will be collected according to the Schedule of Evaluations and Procedures outlined in Table 6-1, Table 6-2, Table 6-3, and Table 6-4:

- Hematology

Hemoglobin, hematocrit, erythrocyte count, platelet count, and leukocyte count with differential

- Serum chemistry

Albumin; alkaline phosphatase; ALT; amylase; AST; total, direct, and indirect bilirubin; blood urea nitrogen; calcium; chloride; total-cholesterol; C-reactive protein; creatinine; creatinine clearance; gamma glutamyl transferase; glucose; lipase; magnesium; phosphate; potassium; sodium; triglycerides; and uric acid

- Urinalysis

Blood, glucose, leucocytes, microscopic, pH and osmolality, protein, and sodium

- Pregnancy test

Urine pregnancy test (women of childbearing potential [WOCBP] only)

- Antibodies to teduglutide and ECP

Blood samples for analyses of antibodies to teduglutide and to ECP will be collected at baseline and at Weeks 12 and 24 (or early termination) during Stage 2 of the study; at Months 6, 12, 18, and 24 (or early termination) during Stage 3; and at every other visit (every 6 months) and end-of-study (or early termination) visit during Stage 4. Blood sample for antibody testing is to be collected at study site prior to first investigational product administration. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing.

Antibody testing is a 3-step process. If a sample tests negative, no further testing is done. If a sample tests positive, further testing is done for teduglutide-specific antibodies. If teduglutide-specific antibodies are detected, the test is deemed "positive" and the titer derived, and neutralizing antibody testing is done. Subjects who test positive for teduglutide-specific antibodies may remain on treatment and blood samples for antibody testing will continue to be collected as per protocol schedule.

Blood samples for anti-teduglutide antibody testing may be stored and then analyzed together periodically to streamline the testing procedure. However, if an investigator suspects that a subject is experiencing an AE that may be associated with the development of anti-drug antibodies, relevant samples will be tested for the presence of anti-drug antibodies upon request.

6.2.6 Plasma Citrulline

Plasma citrulline will be measured as an assessment of enterocyte mass, according to the Schedule of Evaluations and Procedures (Table 6-2, Table 6-3, and Table 6-4). If peripheral venous access is not possible, blood samples for citrulline may be drawn from a central line. The samples will be processed according to instructions in the laboratory manual.

6.2.7 Women of Child Bearing Potential

Women of childbearing potential who are younger than 55 years or are not surgically sterile must have a negative urine pregnancy test result at screening and baseline to be enrolled. Pregnancy tests will also be performed at each on-treatment study visit. Sexually active WOCBP and partners of male subjects must use highly effective and medically acceptable methods of birth control during and for 30 days after the treatment period (ie, abstinence, oral contraceptive pills with barrier methods and spermicide, transdermal or injectable contraceptives, intrauterine device, surgical sterilization of partner), in a manner such that the risk of failure is minimized. The investigator will discuss which methods the subject will prefer to use. For a woman to be considered postmenopausal, at least 2 years must have elapsed since her last menses.

At the time of signing the ICF, WOCBP must be advised of the importance of avoiding pregnancy during trial participation, and the potential risk factors for pregnancy. Male subjects must be advised that their partners must use medically acceptable methods of birth control during and for 30 days after the treatment.

6.2.8 48-Hour Oral Fluid Intake and Urine Output

Subjects will be provided with urine collection containers (as needed) in order to collect 48-hour urine during the 2 days prior to each study visit at which this is required (all visits during

Stages 1 and 2), and at the visits specified in Table 6-3 (Stage 3) and Table 6-4 (Stage 4). The center staff will contact the subject at least 48 hours before the scheduled visits to remind the subject to start measuring I/O, and to record these measurements into the diary. At these times of 48-hour measurements, oral fluid intake must remain as stable as possible compared with baseline. These measurements will also be collected at all interim safety visits.

6.2.9 Clinical Assessment of Crohn's Disease Activity

Any subject enrolled in the study with a history of Crohn's disease will have clinical status assessed at screening and again at the baseline visit in Stage 2 to determine whether the subject has active or quiescent disease. Subjects with active Crohn's disease are excluded from study participation; therefore, endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease. In addition, upper GI contrast series with small bowel follow-through is required in subjects with a history of Crohn's disease to detect any clinically significant active stenosis and/or active stricturing that may need to be addressed.

6.2.10 Subject Diaries

Subjects will be required to record their 48-hour oral/enteral dietary intake, PN/I.V. support (volume), drug dosing (as applicable), and urine output on paper diaries throughout the screening, optimization and stabilization periods, and the treatment periods in Stages 2 to 4 of the study. Diaries should be distributed initially at the time the subject signs consent. Subjects should be instructed to record the 48-hour oral intake/urinary output prior to the screening visit (Visit 1.0) in order to assess their eligibility for stabilization.

6.2.11 Changes in PN/I.V. Volume

The PN and I.V. fluid volumes and constituents are prescribed by the physician. The actual PN and I.V. fluid administered since the last visit will be recorded daily in a paper diary by the subject or designee. Designee may enter data on behalf of the subject if he/she is physically unable to enter data on his/her own. If the subject has a TEAE that prevents him or her from adhering to study requirements, including PN/I.V. volume adjustments, the subject may be withdrawn from the study (Section 4.4.1).

Physician-directed changes in a subject's PN/I.V. volume must be followed by an interim safety visit 5 to 7 days after the scheduled visit when a reduction has taken place. Subjects should be instructed to perform a 48-hour I/O collection during the 48 hours before the interim safety visits in Stages 2 to 4 of the study. At the interim visits the PN/I.V. will be changed if the previous adjustment was not tolerated.

6.2.12 Medical History and Demographics

Information on medical history and demographic data is to be recorded on the appropriate CRF.

6.2.13 Concomitant Medication Assessment

The subject's usage of concomitant medication will be recorded during screening and assessed at each scheduled visit for the duration of the study. The details of any medications and changes therein (change in medication or dosage of medication) will be recorded on the CRF. Any

diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the CRF.

6.2.14 Physical Examinations

Physical examinations will consist of assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities and respiratory, GI, musculoskeletal, cardiovascular, nervous and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. A full physical examination is to be performed at screening and at the first and last visits of Stage 2 and Stage 3, and at every scheduled visit and end-of-study (or early termination) visit of Stage 4. A brief examination of the GI and cardiovascular systems will be made at all other study visits. Other body systems will be examined as clinically indicated.

6.2.15 Vital Signs and Body Weight

Vital signs will be measured according to the Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, Table 6-3, and Table 6-4). Vital signs will include systolic and diastolic blood pressure (mmHg), pulse (beats/minute), and body temperature (ºC) after the subject has been sitting for 5 minutes. Body weight (kg) and BMI also will be recorded. Height will be recorded at screening and at the initial visits of Stages 2 and 3.

Any clinically significant changes (in the opinion of the investigator) noted in vital signs assessments, should be recorded on the appropriate AE page of the CRF. This will assist the sponsor or designee in collecting additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

6.2.16 Electrocardiograms

A 12-lead ECG will be performed during screening, at baseline, Week 4, and at last (Week 24) visits during Stage 2; at first visit (last visit for Stage 2) and at Months 2, 6, 12, 18, and 24 (or early termination) visits during Stage 3; and at end-of-study (or early termination) visit during Stage 4. The ECG will be done at the study center after the subject has been resting for at least 5 minutes. Results will include general findings only (normal/abnormal). Investigators are responsible for providing their own interpretation of the ECG and this will be captured on the CRF.

Two ECG tracings should be printed, and both signed and dated by the investigator. One tracing will be kept with the subject's source documents and the second will be sent to the sponsor or designee. If 2 tracings cannot be printed, the copy will be kept at the site and the original sent to the sponsor or designee.

6.2.17 Gastrointestinal-specific Testing

Gastrointestinal testing will be done for all subjects during the screening period. Follow-up testing will be performed as necessary according to the guidelines noted below. See Schedule of Evaluations and Procedures (Table 6-1, Table 6-2, Table 6-3, and Table 6-4) for details and scheduling.

6.2.17.1 Colonoscopy/Sigmoidoscopy

A colonoscopy/sigmoidoscopy of the remnant colon with polyp removal will be performed prior to teduglutide exposure (during stabilization) in subjects with any colon remnant including rectal stump evaluation. This will be repeated at Visit 10 in Stage 2, at Visit 25 (Month 24 or early termination) in Stage 3, and at end-of-study (or early termination) visit in Stage 4. A colonoscopy is required at the beginning of the study, at the end of the 24-week and 24-month treatment periods, and at the end of the study to determine if any clinically significant changes have occurred. The date and result of colonoscopy are to be recorded in the CRF. If a subject had a normal colonoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

6.2.17.2 Abdominal Ultrasound and Upper GI Contrast Series with Small Bowel Follow-through

An abdominal ultrasound will be performed prior to teduglutide exposure (during stabilization) if this procedure was not performed during the 6 months prior to screening (however, the results of the procedure must be documented). Upper GI contrast series with small bowel follow-through will be required for all subjects with a history of Crohn's disease and will be performed during the stabilization period, prior to the baseline visit.

6.3 Pharmacokinetic Evaluations

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0) in Stage 2 of the study. Samples for PK analysis will be collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7.

The following parameters will be derived:

- AUC_{0-inf}
- AUC_{0-t}
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V/F

6.4 Schedule of Evaluations and Procedures

All clinical study evaluations prior to treatment with teduglutide will be performed according to the Schedule of Evaluations and Procedures – Stage 1, Table 6-1. All clinical study evaluations during the first 24 weeks of treatment will be performed according to the Schedule of Evaluations and Procedures – Stage 2, Table 6-2. All clinical study evaluations during the extension will be performed according to the Schedule of Evaluations and Procedures in Stage 3 (Table 6-3) and Stage 4 (Table 6-4).

Subjects who drop out of the study prior to the final visit should have all early termination procedures done whenever possible.

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Informed consent	X[a]	X					
Eligibility criteria		X					
Medical history, demographics		X					
Crohn's disease assessment		X					
Physical examination[b]		X					
Evaluation of PN/I.V. volume		X	X	X	X	X	X[c]
Adverse events		X	X	X	X	X	X
Abdominal ultrasound[d]							X
Upper GI contrast series with small bowel follow-through[e]							X
Colonoscopy/sigmoidoscopy of remnant colon[f]							X
Concomitant medication[g]		X	X	X	X	X	X
Vital signs		X	X	X	X	X	X
Height		X					
Body weight and BMI		X	X	X	X	X	X[h]
12-lead ECG		X					
Safety laboratory tests		X	X	X	X	X	X
Urine pregnancy test		X					
Interim safety evaluation		[X][i]	[X][i]	[X][i]	[X][i]	[X][i]	
Diary	X[a]	X	X	X	X	X	X
Review 48-hour oral fluid intake[j] (Diary)		X	X	X	X	X	X

Table 6-1 Schedule of Evaluations and Procedures – Stage 1

Procedures	Prior to screening	Screening (7-day maximum)	PN/I.V. Optimization Period (8-week maximum)				PN/I.V. Stabilization Period 4-8 weeks (± 7 days)
			Week 2 (± 3 days)	Week 4 (± 3 days	Week 6 (± 3 days)	Week 8 (± 3 days)	
Visit Number:		**V1.0**	**V1.1**	**V1.2**	**V1.3**	**V1.4**	**V1.5**
Review 48-hour urine output[j] (Diary)		X	X	X	X	X	X
Optimization assessment[k]		X	X	X	X	X	

BMI = body mass index; ECG = electrocardiogram; GI = gastrointestinal; ICF = Informed Consent Form; PN/I.V. = parenteral nutrition/intravenous fluids; V = visit

Note: One repeat of the optimization/stabilization periods combined is permitted.

[a] The ICF is to be distributed to the subject for review. Once the ICF has been signed by the subject, the diary should be given to the subject in order to record the 48-hour intake/output measurements. No study-related procedures are to be performed unless the ICF has been signed.

[b] A full physical examination is to be performed at screening.

[c] PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[d] Abdominal ultrasound should be completed during the stabilization period, prior to the baseline visit if not performed within 6 months prior to screening.

[e] Upper GI contrast series with small bowel follow-through is required for subjects with Crohn's disease. This should be completed during the stabilization period, prior to the baseline visit.

[f] Colonoscopy/sigmoidoscopy of remnant colon with polyp removal before teduglutide exposure will be performed in subjects with any colon remnant including rectal stump evaluation. Colonoscopy should be completed during the stabilization period, prior to the baseline visit, if required. If a subject had a normal colonoscopy/sigmoidoscopy within 6 months prior to screening, a baseline colonoscopy/sigmoidoscopy will not be required.

[g] At screening, information on all medications taken in the previous 30 days will be collected.

[h] This is the first of 2 body weight measurements that will be used to determine drug volume.

[i] Interim safety evaluations will be assessed **5 to 7 days** after any scheduled visit **only if a PN/I.V. change** was made. These measures include 48-hour oral fluid intake, 48-hour urine volume, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[k] The optimization assessment should be made by reviewing the 48-hour oral fluid intake and urine output from the Diary and assessing whether the subject meets the optimization criteria as described in the protocol.

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (days)		± 2	± 3	± 3	± 5	± 5	± 5	± 7	± 7
Eligibility criteria	X								
Crohn's disease assessment[c]	X								
Physical examination[d]	X		X	X	X	X	X	X	X
Evaluation of PN/I.V. (actual volume L/week)	X[e]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Colonoscopy/ Sigmoidoscopy									X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
Body weight and BMI	X[f]		X	X	X	X	X	X	X
Height	X								
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Antibodies to teduglutide and *E. coli* protein[g]	X					X			X
PK sampling	X[h]	(X)	(X)	(X)	(X)	(X)			
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X	X	X	X	
Interim safety evaluation			[X][i]	[X][i]	[X][i]	[X][i]	[X][i]	[X][i]	
48-hour oral fluid intake[j] (Diary)	X		X	X	X	X	X	X	X
48-hour urine output[j] (Diary)	X		X	X	X	X	X	X	X
Diary	X	X	X	X	X	X	X	X	X
Teduglutide dosing[k]	X	X	X	X	X	X	X	X	X
Compliance[l]		X	X	X	X	X	X	X	X

Table 6-2 Schedule of Evaluations and Procedures – Stage 2

Procedures	Baseline	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early termination[b])
Visit Number:	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Day	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**

(X) = Possible PK sampling time point (Refer to footnote "i".); [X] = Possible interim safety evaluation time point (Refer to footnotes "f" and "g".);
BMI = body mass index; 48-hour I/O = 48-hour fluid intake/urine output; ECG = electrocardiogram; PK = pharmacokinetic; PN = parenteral nutrition;
PN/I.V. = parenteral nutrition/intravenous fluids; V = visit

[a] Subject does not have to visit the clinic for visit. Assessments will be completed over the phone.

[b] Subjects with an early termination visit should have all applicable Visit 10 assessments. Call sponsor for guidance.

[c] Subjects with active Crohn's disease are excluded from the study participation, therefore endoscopy/colonoscopy prior to study treatment may be required in subjects with clinical suspicion of active disease.

[d] A full physical examination is to be performed at baseline and Visit 10; a brief examination will be performed at all other dosing weeks with a clinic visit.

[e] The PN/I.V. evaluation is to confirm weekly volume for Inclusion Criteria 5 (PN/I.V. frequency) and 6 (stable PN/I.V.).

[f] This is the second of 2 body weight measurements that will be used to determine drug volume.

[g] Blood sample for antibody testing is to be collected at baseline (Visit 2) prior to first investigational product administration. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing.

[h] Samples for PK analysis are collected pre-dose, at 15, 30 and 60 minutes post-dose and at 2, 3, 4, 6, 8, 10 and 12 hours post-dose. If PK sample collection is missed at Visit 2, PK sample may be collected at any visit through Visit 7. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

[i] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. These measures include 48-hour oral fluid intake, 48-hour urine output, hematocrit, serum blood urea nitrogen and creatinine, and urine sodium.

[j] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN is infused daily.

[k] Subjects will be trained to self-inject teduglutide at baseline on Day 0 (Visit 2). The first injection should be administered under the supervision of the investigator or designee and the subject observed for at least 4 hours. Subjects will then self-inject the study drug at home. Dosing should not take place at early termination visit.

[l] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13[b]	Mo 2/14	Mo 3/15[b]	Mo 4/16	Mo 5/17[b]	Mo 6/18	Mo 7/19[b]	Mo 8/20	Mo 9/21[b]	Mo 10/22	Mo 11/23[b]	Mo 12	Mo 24 (or early termi-nation)
Visit Number:	V1	V2/ 14	V3/ 15	V4/ 16	V5/ 17	V6/ 18	V7/ 19	V8/ 20	V9/ 21	V10/ 22	V11/ 23	V12/ 24	V13	V25
Visit Window (days)		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Eligibility, Informed consent	X													
Reproductive status (female subjects)	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X		X		X		X		X		X		X	X
Physical examination[c]	X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X	X
Body weight and BMI	X		X		X		X		X		X		X	X
Height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X		X		X		X		X		X		X	X
12-lead ECG	X		X[d]				X						X	X
Colonoscopy/sigmoidoscopy of remnant colon														X
Citrulline	X		X		X		X		X		X		X	X
Antibodies to teduglutide and *E. coli* protein[e]	X						X						X	X
Drug dispensing	X		X		X		X		X		X		X	X[f]
Interim safety visit	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]	[X][g]
Diary[h]	X		X		X		X		X		X		X	X
48-hour oral fluid intake[i] (Diary)	X	[X]	X	[X]	X	[X]	X	[X]	X	[X]	X	[X]	X	X
48-hour urine output[i] (Diary)	X	[X]	X	[X]	X	[X]	X	[X]	X	[X]	X	[X]	X	X

Table 6-3 Schedule of Evaluations and Procedures – Stage 3 (Extension)

Procedures	First Visit[a] (last visit for Stage 2)	Mo 1/13[b]	Mo 2/14	Mo 3/15[b]	Mo 4/16	Mo 5/17[b]	Mo 6/18	Mo 7/19[b]	Mo 8/20	Mo 9/21[b]	Mo 10/22	Mo 11/23[b]	Mo 12	Mo 24 (or early termi-nation)
Visit Number:	V1	V2/ 14	V3/ 15	V4/ 16	V5/ 17	V6/ 18	V7/ 19	V8/ 20	V9/ 21	V10/ 22	V11/ 23	V12/ 24	V13	V25
Visit Window (days)		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Evaluation of PN/I.V. (actual volume L/week)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Teduglutide dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]
Compliance[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[X]=optional 48-hour oral fluid intake and urine output (Diaries) to be measured at the discretion of the investigator in consideration of PN/I.V. adjustment; [X][g]=possible interim safety evaluation time point (Refer to footnote "g".); BMI=body mass index; ECG=electrocardiogram; L=liter; Mo=month; PN/I.V.=parenteral nutrition/intravenous fluids; V=visit

Note: Study visits will be scheduled every other month throughout the study period. At the end of 12 months, the visit schedule will repeat starting with the Month 1 visit. Interim (standard of care) visits may be utilized to assess subjects' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] In case study extension treatment cannot be started at the last completed visit of Stage 2 for any reason, the investigator may repeat any assessments as deemed appropriate.

[b] Subject does not need to visit the clinic. Assessments will be completed over the telephone.

[c] Full physical examination to be performed at first and last visits; a brief examination will be performed at all other study visits.

[d] An ECG will be taken at Visit 3, but not at Visit 15.

[e] Sample for antibody testing must be drawn at least 14 hours after dosing.

[f] Teduglutide dispensing and dosing should not be performed at early termination visit.

[g] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[h] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[i] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily or the subject achieves enteral autonomy (no PN/I.V. use).

[j] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

Table 6-4 Schedule of Evaluations and Procedures – Stage 4 (Extension)

Procedures	Every 3-Month Visit[a]	EOS (or early termination)
Visit Number:	**V26, 27, 28, etc.**	**EOS**
Visit Window (days)	**± 7**	**± 7**
Adverse events	X	X
Urine pregnancy test	X	X
Physical examination[b]	X	X
Vital signs	X	X
Body weight and BMI	X	X
Concomitant medications	X	X
Safety laboratory tests	X	X
12-lead ECG		X
Colonoscopy/sigmoidoscopy of remnant colon		X
Citrulline	X	X
Antibodies to teduglutide and *E. coli* protein[c]	(X)	X
Drug dispensing	X	
Interim safety visit	[X][d]	[X][d]
Diary[e]	X	X
48-hour oral fluid intake[f] (Diary)	X	X
48-hour urine output[f] (Diary)	X	X
Evaluation of PN/I.V. (actual volume L/week)	X	X
Teduglutide dosing	X[g]	
Compliance[h]	X	X

(X)=assessment to be performed only every other visit (every 6 months); [X][d]=possible interim safety evaluation time point (Refer to footnote "d"); BMI=body mass index; ECG=electrocardiogram; EOS=end of study; L=liter; PN/I.V.=parenteral nutrition/intravenous fluids; V=visit

Note: Study visits will be scheduled every 3 months throughout the Stage 4 period. Interim (standard of care) visits may be utilized to assess subjects' well-being (ie, occurrence of adverse events) and to check for any changes in medications.

[a] Subjects will undergo a clinic visit every 3 months until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

[b] Full physical examination to be performed at end-of-study (or early termination) visit; a brief examination will be performed at all other study visits.

[c] Sample for antibody testing must be drawn at least 14 hours after dosing. To be collected at every other visit only (every 6 months) and end-of-study (or termination) visit.

[d] Interim safety evaluations will be performed 5 to 7 days after any scheduled visit when a reduction has been made to the subject's PN/I.V. volume. Hematocrit, serum blood urea nitrogen and serum creatinine, and urine sodium will be measured.

[e] The diary is to be completed for the 2-week period prior to every clinic or telephone visit.

[f] All subjects will measure 48-hour oral fluid intake and urine output at home immediately prior to the next scheduled visit and interim safety visit. The measurements should include 1 day on and 1 day off PN/I.V., unless PN/I.V. is infused daily or the subject achieves enteral autonomy (no PN/I.V. use).

[g] The dose of study drug administered at time of entry into Stage 4 (Visit 26) may be adjusted based on change in the subject's weight from baseline.

[h] Compliance will be checked at every visit by asking subjects if they have taken their study drug according to instructions and by performing drug accountability.

7 DATA MANAGEMENT

7.1 Data Collection

Upon entry into the study (informed consent signed), all subjects will be assigned an eight-digit subject number. The first 4 digits consist of the study site number. The last 4 digits will be assigned sequentially starting with 0001. This number is the main identifier for subjects.

The site staff will keep records of the subject's visit in the files considered as source documents for that site (eg, hospital chart, research chart, etc.). Source data are all information contained in original records of clinical findings, observations, or other trial-related activities necessary for evaluation and reproducibility of data (eg, progress notes, hospital records, computer print-outs, screening logs, and recorded data from automated instruments). In case of computerized source data, the investigator has to give the sponsor access to the subject files at each monitoring visit. The data is then entered into the Electronic Data Capture System, RAVE. To ensure that data have been entered correctly on the electronic case report forms (eCRF), they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. The investigator or designee will be responsible for the timely recording of subject data into the eCRF.

The investigator and study site must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents.

The principle investigator (PI) or designee will review all eCRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will sign the eCRF via an electronic signature. The PI will be responsible for reviewing the data in a timely manner. Non-CRF data will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database.

Paper diaries will be used by the subjects to record study information, which includes PN/I.V. infusions, drug dosing, and 48-hour I/O. Standardized procedures will be used to incorporate these data into the clinical database.

The sites will be provided with CRF guidelines outlining the specific procedures to use when entering the data into the Electronic Data Capture System. Data validation and edit checks will be conducted on the data. Any discrepancies will generate queries that should be resolved at the study site in a timely manner. The audit trail will be recorded in the data base.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical according to the clinical study protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledges that all data are acceptable, the data will be declared a "clean file," and the data will be frozen/locked.

An audit of the clinical database will be performed. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be ready for statistical analysis by the sponsor or designee.

7.2 Record Retention

All source documents, records, and reports will be retained by the clinical center/investigator in accordance with ICH guidelines. These documents include all primary data or copies thereof (eg, laboratory records, ECGs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report.

All source documents, records, and reports should be retained for a period of not less than 15 years from completion of the clinical trial. The sponsor will notify site staff of permission to dispose of them.

7.3 Quality Control

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical classification) and preferred name using the World Health Organization Drug Dictionary.

The study data will be captured by the investigational site staff on CRFs. The staff will keep records of the subject's visit in the files considered as source documents for that site.

Study information on PN/I.V. infusions and 48-hour I/O will be recorded by the subjects in subject diaries. These data are regarded as source data and will remain at the site. The relevant information will be recorded in the CRF at each study visit.

To ensure that data have been entered correctly on the CRF, they will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding any questions or discrepant data. Data validation and edit checks will be conducted by the sponsor or designee. Any discrepancies noted will generate queries. Upon receipt of the query via the electronic data capture (EDC) system, the site will research the issue identified on the query and record the answer in EDC. In the event that the appropriate individual at the site provides an incorrect, incomplete, or inappropriate response, the query will be re-issued to the site. When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the site, the data will be evaluated for quality purposes. A clean file of the data is defined as when the data in the database and the reference values are complete and logical according to the protocol, general guidelines, and data management plan. Once the sponsor or designee acknowledge that all data are acceptable, the data will be declared a "clean file," and the database will be frozen/hard locked. At the end of the study, each site will receive a compact disc containing their data.

8 STATISTICAL METHODOLOGY

8.1 Demographic and Baseline Variables

Demographic variables include age; gender; race; height; body weight; BMI; intestinal length; presence or absence of a stoma, colon in continuity, ileocecal valve; and time since last surgical resection.

Descriptive statistics (eg, number, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the baseline and demographic characteristics. Individual data will also be listed.

8.2 Efficacy and Pharmacodynamic Variables

No formal testing will be conducted for efficacy or pharmacodynamic variables. For continuous variables, descriptive statistics will be used to summarize median, maximum, minimum, mean (± standard deviation [SD]), geometric mean (± standard error [SE]) and its 95% confidence interval (CI). For categorical variables n (%) will be summarized. Listings of individual data will be summarized.

PK parameter estimates will be calculated using a non-compartmental analysis.

8.2.1 Efficacy and Pharmacodynamics – Stage 2

The efficacy endpoints are:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and EOT). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24 in Stage 2 of the study (responder). A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline from baseline to Week 24 (or EOT)

In this uncontrolled study, efficacy will be described by the following assessments:

- Comparison of the mean PN/I.V. percent change at Week 24 with the upper limit of the 95% CI (of least square [LS] mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.
- Comparison of the upper limit of the 95% CI of the mean percent change in weekly PN/I.V. volume at Week 24 with the mean change in PN/I.V. volume at Week 24 in the placebo group in Study CL0600-020. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from Study CL0600-020. The comparison should take

into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.

- Comparison of the mean PN/I.V. percent change at Week 24 with the lower limit of the 95% CI (of LS mean) for the teduglutide group in pivotal Phase 3 Study CL0600-020 at Week 24. As Study TED-C14-004 is an uncontrolled study, PN/I.V. results will be compared with those from US/EU pivotal controlled Phase 3 Study CL0600-020. The comparison should take into account the anticipated variability of the data due to the small number of subjects in Study TED-C14-004.
- Comparison of the responder rate with the primary endpoint responder rate of the placebo group observed in Study CL0600-020. (The percentage of subjects who achieved ≥ 20% PN/I.V. reduction from baseline at Week 20 and Week 24 in the placebo group was 30.2%.)
- Evaluation of the change in days off PN/I.V. per week. In general, day(s) off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.
- Evaluation of the number of subjects who achieve complete enteral autonomy (wean off) of PN/I.V. during the study. In general, weaning off PN/I.V. cannot be expected in this subject population, which has required long-term PN/I.V., unless absorption is increased by teduglutide.

8.2.2 Efficacy and Pharmacodynamics – Stages 3 and 4

Absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

8.3 Safety

The safety and tolerability of teduglutide treatment will be assessed by evaluation of TEAEs, 12-lead ECGs, vital signs, GI-specific testing, laboratory safety data, antibodies to teduglutide, and changes in urine output, body weight, and BMI. See Section 6.2 for a full list of safety variables.

8.3.1 Statistical Methods for Safety Variables

Adverse events will be coded using the most recent version of the MedDRA dictionary. Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity, relationship to treatment, AEs leading to discontinuation, and AEs leading to death. SAEs will also be tabulated by overall and treatment-related events.

For laboratory tests, 48-hour urine output, vital signs, body weight, BMI, and ECG variables, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from Baseline at each time point.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

8.4 Pharmacokinetic Variables – Stage 2 Only

Single-dose PK will be evaluated on the first day of teduglutide treatment (Day 0). Pharmacokinetic variables include AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V/F. Pharmacokinetic parameter estimates will be calculated using a non-compartmental analysis.

8.5 Analysis Populations, Data Sets, and Time Points

8.5.1 Analysis Populations

The intent-to-treat (ITT) population is defined as any subjects who were enrolled into the study and eligible to enter stage 2. The safety population is defined as the subset of ITT with subjects who received at least one administration of study drug with any safety follow up. The primary population analyzed for efficacy will be the ITT population. An additional per-protocol population analysis may also be performed as secondary/sensitivity analysis. Applicable analysis populations will be defined in the Statistical Analysis Plan (SAP).

8.6 Statistical/Analytical Issues

8.6.1 Adjustments for Covariates

No baseline stratification parameter is employed in this study.

8.6.2 Handling of Dropouts or Missing Data

All subjects enrolled will be included in the analyses. Missing safety parameters will not be imputed. The weekly PN/I.V. volume recorded in the subject diaries will be calculated in 2-week intervals. Missing daily PN/I.V. volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, or else the interval will be classified as missing. Details for the imputation algorithm for the missing endpoint values for PN/I.V. volume will be detailed in the SAP.

8.6.3 Interim Analyses

An interim analysis of study data will be done at the completion of the 24-week Stage 2 part of the study and again after subjects complete 6 months of treatment in the Stage 3 extension period (1 year of teduglutide exposure). A final analysis of study data will be done at the end of the study.

8.6.4 Multiple Comparisons/Multiplicity

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.6.5 Use of an Efficacy Subset of Subjects

All subjects will be included in the analysis.

8.6.6 Examination of Subgroups

Not applicable

8.7 Determination of Sample Size

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

8.8 Changes to Planned Statistical Analyses

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final Clinical Study Report (CSR).

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 [5th revision], Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004, and Seoul [6^{th} revision]).

In accordance with guidelines, the protocol, any advertisements, and ICFs (or assent form, if applicable) will be reviewed and approved by the IRB. The sponsor will supply relevant materials for the investigator to prepare a written ICF and submit to the IRB for the protocol/ICF's review and approval. Verification of the IRB approval of the protocol and the written informed consent statement will be forwarded to the sponsor (or designee).

The investigator will inform the IRB of subsequent protocol amendments and any SUSARs if the sponsor has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator. The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

9.2 Subject Information and Consent

In accordance with applicable guidelines, informed consent shall be documented by the use of a written subject information/ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed. When the subjects are under 20 years old, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s) after confirming assent from the subject. A subject information/ICF model will be provided by the

sponsor or designee and adapted by the investigator in agreement with the sponsor to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study and the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

9.3 Subject Data Protection

All data provided to the sponsor or designee will be identified only by subject number and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Site-specific information must be added to the ICF as appropriate.

Subjects should also be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records (relevant to the study), including medical history, for data verification.

The PI is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and a secondary unique identifier (ie, hospital/clinic number).

9.4 Payment and Compensation

The special or specified medical care system covers the treatment periods. The sponsor and the trial site will discuss payment for cooperating in this clinical trial. IRB-approved expenses will be paid by the sponsor to the subject thorough the trial site.

The sponsor will provide insurance or indemnify the subject against claims arising from this clinical trial, except for claims that arise from malpractice and/or negligence.

9.5 Changes to the Protocol

No change in the study procedures shall be affected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the study reference manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the PI and those concerned within the conduct of the study. The sponsor and PI are responsible for reporting all amendments to the IRB.

9.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

This clinical study will be registered on www.ClinicalTrials.gov and the results will be disclosed on www.ClinicalStudyResults.org.

9.7 Study Termination

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

10 REFERENCES

None

APPENDIX 1 PN/I.V. OPTIMIZATION (STAGE 1)

After signing the ICF, the investigator will determine if the subject's PN/I.V. volume produces an appropriate urine output target of 1.0 to 2.0 L/day. If the output is within the range, the subject will enter the stabilization period. If the output is outside the range, the subject's PN/I.V. volume should be adjusted appropriately to reach the targeted urine output of between 1.0 to 2.0 L/day while keeping the subject adequately hydrated and nourished. For example, if 48-hour urine output is:

- < 1.0 L/day, then PN/I.V. should be increased.
- > 2.0 L/day, then PN/I.V. should be reduced.

If it is not possible to keep the subject adequately hydrated and nourished within the targeted urine output range, the minimally tolerated PN/I.V. volume should be documented. Keep in mind the following:

- Total weekly PN/I.V. volume can be adjusted by up to 30% of the current volume.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet (eg, at least 1.3 times the estimated basal metabolic rate).

Steps for adjusting PN/I.V. volume:

1. **Screening and Optimization Visits:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home immediately prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily. Blood and urine samples will be collected at each visit to evaluate hydration and nutrition. All blood and urine samples should be taken at a consistent time period throughout the study that is convenient for the subject and site staff.

2. **Interim Safety Evaluations:** If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed after 5 to 7 days of the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

3. Maintain the PN/I.V. level until the next scheduled optimization visit.

4. Repeat steps 1 through 3 until the subject achieves an optimized volume of PN/I.V. indicated by targeted urine output of 1.0 to 2.0 L/day. If a subject has not achieved an optimal tolerated volume of PN/I.V. after 8 weeks, consult the sponsor's Medical Monitor.

5. **PN/I.V. Stabilization:** Once an optimal tolerated PN/I.V. volume has been reached, the subject will begin the 4-week minimum stabilization period. No further PN/I.V. adjustments should take place during this time period.

APPENDIX 2 PN/I.V. ADJUSTMENT DURING DOSING (MAIN TREATMENT PERIOD – STAGE 2)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- There will be no PN/I.V. reduction attempts at baseline and Week 1.
- PN/I.V. reductions target urine output increases of at least 10% over baseline.
- Attempts to reduce PN/I.V. will be made at dosing Weeks 2, 4, 8, 12, 16, and 20.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **stabilized baseline PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A2-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with baseline oral intake.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Frequent checks will be made to ensure the adjustments are safe (see Table A2-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo 1 additional attempt to reduce volume by at least 10%.
- Subjects who fail to maintain a PN/I.V. reduction due to a medical necessity (eg, sepsis or hospitalization due to an AE) will not be considered a failure of reduction.
- If at any time, the algorithm cannot be followed, consult with the sponsor's Medical Monitor.

Table A2-1 PN/I.V. Adjustments based on 48-hour Urinary Output

Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% (Week 2) or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A2-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. – parenteral nutrition/intravenous (volume)

Table A2-2 Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
*AND consistent with subject's previous levels prior to study entry.
Note: In combination with Table A2-1, any one of the above criteria determines dehydration.
Note: If weight gain of ≥1.5 kg, request physician review.

Steps for adjusting PN/I.V. volume:

1. **DOSING WEEKS 2, 4, 8, 12, 16, and 20:** Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily or achieves enteral autonomy (no PN/I.V. use). Blood and urine samples will be collected to evaluate hydration and nutrition (see Table A2-2). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. **PN/I.V. Changes:** Review Table A2-1 and Table A2-2 to take appropriate action. (Reduction of PN/I.V. by 10% or more of the baseline volume is called a "challenge.")

3. **Interim Safety Evaluations:** If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment (see Table A2-3), accompanied by determination of 48-hour I/O and symptoms of dehydration. At the interim safety visit, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit.

Table A2-3 Targeted PN/I.V. Adjustments at Interim Visits

Urine Output, Hydration and Nutrition	PN/I.V. Action
Output less than Baseline	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is dehydrated (See Table A2-2)	Increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is not dehydrated, but is inadequately nourished (See Table A2-2)	If possible, maintain PN/I.V. volume and increase nutrition. If not, increase PN/I.V. to previous volume[a]
Baseline output or greater and subject is adequately hydrated and nourished (See Table A2-2)	Maintain PN/I.V.

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume)
[a] If most recent reduction was greater than 10% due to a urine volume of more than 2 L/day, a more moderate increase in PN/I.V. is allowed.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

   a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

   b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

   c. Subjects who did not tolerate the reduction may be re-challenged at the next visit provided they meet the criteria for adequate hydration and nutrition.

   d. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

APPENDIX 3 PN/I.V. ADJUSTMENT DURING DOSING (EXTENSION TREATMENT PERIOD – STAGE 3 AND STAGE 4)

Points to keep in mind when adjusting PN/I.V. volume during dosing:

- PN/I.V. volume reductions target urine output increases of at least 10% over Baseline. Baseline measurements for all subjects are taken at the **baseline of study main treatment period**.
- Considerations to reduce PN/I.V. will be made at all planned visits.
- PN/I.V. adjustments are targeted to be at least 10% but no more than 30% of **STABILIZED BASELINE PN/I.V.** level.
- Adjustments should be based on the actual PN/I.V. volume the subject infuses. Subjects should remain compliant with the PN/I.V. prescription during the length of the study.
- PN/I.V. constituents may be adjusted at the discretion of the investigator.
- Criteria for PN/I.V. adjustments are in Table A3-1.
- During the 48-hour I/O measurement period, oral intake should be consistent with Baseline oral intake or greater.
- If there is a change in oral intake, the investigator should consider this when adjusting the PN/I.V. volume.
- Subjects should be encouraged to maintain a stable normal or hyperphagic diet.
- Checks will be made to ensure the adjustments are safe (see Table A3-2).
- Subjects who fail to maintain a PN/I.V. reduction may undergo additional attempts to reduce volume by at least 10%.
- If at any time, the algorithm cannot be followed, consult with the sponsor's Medical Monitor.

Table A3-1 PN/I.V. Adjustments Based on 48-hour Urinary Output

48-hour Urine Output	PN/I.V. Action
Below 1.0 L/day or target based on stabilized urine output	Increase PN/I.V. by at least 10% or to previous level.
1.0 L/day or more and less than Baseline	If subject is dehydrated or inadequately nourished (see Table A3-2), increase PN/I.V. If not, maintain PN/I.V.
Baseline or more, and less than a 10% increase over Baseline	Maintain PN/I.V.
At least a 10% increase over Baseline	Reduce PN/I.V. by at least 10% of stabilized Baseline level up to a clinically appropriate amount (maximum of 30%).

L = liter; PN/I.V. = parenteral nutrition/intravenous (volume)

Steps for adjusting PN/I.V. volume:

1. Subjects will be assessed at planned intervals for hydration and nutrition. The subject will make all measurements of 48-hour I/O at home prior to the scheduled visits. The

measurements should include 1 day on and 1 day off PN/I.V. unless subject infuses PN/I.V. daily or achieves enteral autonomy (no PN/I.V. use). All blood and urine samples should be taken at a consistent time period throughout the study, convenient for the subject and site staff.

2. PN/I.V. CHANGES: Review Table A3-1 and Table A3-2 to take appropriate action.

3. If any PN/I.V. adjustments are made, the clinical effect and the health status of the subject will be assessed 5 to 7 days after the adjustment. Laboratory safety samples should be evaluated following a PN/I.V. adjustment, accompanied by determination of 48-hour I/O and symptoms of dehydration. At **the interim safety visit**, PN/I.V. should be increased if the decrease was not tolerated. No further reductions to PN/I.V. volume are made at the interim safety visit. After the first 3 months of the extension treatment period, the assessment of laboratory values is not mandatory anymore at interim safety visits.

4. Maintain the adjusted PN/I.V. level until the next scheduled visit.

5. Repeat steps 1 through 4 at each study visit as indicated per protocol.

    a. It is preferred that when the total weekly PN/I.V. needs have been reduced to a level that safely allows for a day or days off PN/I.V., the physician should consider instituting a day(s) off PN/I.V.

    b. If the total weekly PN/I.V. is only administered in 2 days, it is probably in the subject's best interest to be weaned off PN/I.V. completely. This is the 1 exception to the maximum 30% reduction guidance. This weaning should be done under the supervision of the investigator.

    c. If the subject experiences symptoms of dehydration, the subject can be advised by the investigator to take extra I.V. fluid that will be included in the weekly PN/I.V. volume total.

Table A3-2 Targeted Criteria for Hydration and Nourishment

Hydration Assessment	Hydration Adequate*
Hematocrit	At or below ULN
Serum BUN	At or below ULN
Serum creatinine	At or below 2xULN
Urine sodium	20 mmol/day or more
Clinical signs and symptoms of dehydration	Absent
Body weight change in 4 weeks	Change less than 1.5 kg

BUN = blood urea nitrogen; ULN = upper limit of normal
* AND consistent with subject's previous levels prior to study entry.
Note: In combination with Table A3-1, any one of the above criteria determines dehydration.
Note: If weight gain of ≥1.5 kg, request physician review.

APPENDIX 4 PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IRB) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or In-country Clinical Caretaker including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To maintain drug records, electronic copies of case report forms, laboratory records, data sheets, correspondence records, and signed subject consent/assent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

_____
Principal Investigator (Print Name)

_____ _____
Principal Investigator (Signature) Date
(DD MMM YYYY)

Shire

MEMORANDUM

TO: Study Investigators and Study Coordinators

FROM: [redacted], MBA
[redacted]
Global Clinical Operations

DATE: 04 OCT 2018

Re: TED-C14-004 Safety Reporting Information

This memorandum revises the **Emergency Contact Information** for Shire Global Drug Safety from what is currently documented on page 2 of the TED-C14-004 Protocol v6.0, Amendment 4: 03 April 2017. This change was initially effective 02 JAN 2018 and updated on 02 OCT 2018.

The new email address of the Shire Global Drug Safety for the reporting of Safety Information is: [redacted] and the fax number is [redacted].

This memorandum does not impact the conduct of the study. Please submit this document to your IRB notifying them of this clarification regarding the Emergency Contact Information for the Shire Global Drug Safety team.

If you have further questions, please do not hesitate to contact your EPS CRA or Shire Directly.

With best regards,

[redacted]
[redacted] MBA
Mobile: [redacted]
Email: [redacted]

cc: TED-C14-004 Study TMF