

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

**1) Protocol Title:**

Teduglutide for treatment of enterocutaneous fistula (ECF) – a pilot study to demonstrate safety, efficacy, and feasibility

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**2) Objectives**

To demonstrate the safety, efficacy, and feasibility of teduglutide in patients with ECF; to evaluate quality of life in patients with ECF receiving teduglutide

**Hypothesis**

We hypothesize that administration of teduglutide to patients with ECF is safe, feasible, and effective in reducing fistula output by 20% and improving quality of life.

**Design**

Open label cross-over pilot study to determine safety and efficacy of teduglutide in patients with ECF. Our planned sample size is 10 subjects randomized and treated with at least 1-dose of study drug .

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

The primary efficacy end point will be decrease in fistula volume by 20% from baseline 3-day average, as measured by the patient.

The secondary efficacy end points will be cessation of fistula output altogether and health-related quality of life questionnaire score as assessed by the questionnaires (see below) at time points Study Visit 5, 10, and 11 (3 months after end-of-treatment).

Subjects that complete both arms of the study who have a favorable (but incomplete) response and are deemed to be reliable (both as determined by the principal investigator) will be offered an open-label extension during which they will continue to receive teduglutide for up to another 12 months or permanent fistula closure, whichever occurs first.

### **3) Background**

Enterocutaneous fistula is (ECF) defined as an abnormal connection between the gastrointestinal tract and the skin, or an open abdomen (enteroatmospheric fistula, EAF). This disease is highly morbid and associated with significant ICU length of stay, hospital stay, and average hospital charges >\$500,000 [1]. Death and complication rates are disproportionately high, with mortality rates commonly reported between 6 to 48% [2]. Survivors with ECF have lower health-related quality of life [3].

The treatment of ECF is challenging and often requires a multi-disciplinary approach including gastroenterologists, surgeons, wound care specialists, and nutritionists. Intestinal rehabilitation for ECF is directed at decreasing ECF output (completely, if possible) and achieving independence from artificial nutrition (enteral or parenteral). There are few pharmacologic options for the treatment of ECF. Somatostatin and its analogues (ex: octreotide) have been the most widely studied, but results are conflicting, with significant effects being found only on meta-analysis [4].

Glucagon-like peptide 2 (GLP-2) is an endogenous hormone secreted by L cells in the intestine which has trophic effects. Exogenous GLP-2 administration stimulates intestinal blood flow, decreases gastric acid secretion, and improves nutrient and fluid absorption in animal models and human studies [5-7].

Teduglutide is a GLP-2 analogue with a much longer half-life than GLP-2. An open label pilot study of teduglutide demonstrated improvements in enteral absorption. At the microscopic level, improvements were seen in small bowel villus height, crypto depth, and mitotic index [8]. In two phase III randomized, placebo-controlled studies, 24 weeks of administration of teduglutide led to significant decreases in PN/IV volume requirements [9, 10]. Small bowel villus height and plasma citrulline (a marker for enterocyte mass) were both significantly improved in the teduglutide groups [9]. This efficacy was not only maintained, but also increased, in long-term extension studies with continued gains and

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

additional patients achieving PN/IV independence. Of the 19 non-responders in the original 24-week study, 11 became responders in the extension study [11]. Approved by the FDA in 2012 for the treatment of adults with short bowel syndrome with intestinal failure (SBS-IF), teduglutide is well-tolerated and common adverse events are mild and related to gastrointestinal symptoms such as abdominal pain, nausea, and vomiting [12].

It is easy to conceive that the results of teduglutide treatment could be extrapolated to patients with ECF. For example, SBS-IF patients treated with GLP-2 experienced a reduction in fecal wet weight of approximately 33% (from 3.0 kg/day to 2.0 kg/day) [7]. Similar changes in ECF could convert high-output fistulas (>500 mL/day) to medium- (200-500 mL/day) or low-output fistulas (<200 mL/day), significantly simplifying fluid/electrolyte management, or even resolve low-output fistulas completely.

#### **4) Entry Criteria**

##### **Inclusion criteria**

- a) Age >18
- b) Enterocutaneous fistula (ECF) that could be secondary to volvulus, injury, prior trauma or surgery, or vascular ischemia

##### **Exclusion criteria**

- a) Perianal fistula
- b) History of radiation enteritis or sprue (as defined by history)
- c) Active (<1 year) alcohol or drug abuse
- d) Significant hepatic, or cardiac diseases as defined as:
  - i. Hepatic: aspartate aminotransferase (AST)  $\geq 2$  times upper limit of normal (10-40 U/L)
  - ii. Cardiac: unstable angina or evidence of active myocardial ischemia (elevated troponin level drawn by clinical suspicion)
- e) Severe renal dysfunction: serum creatinine  $\geq 2$  times upper limit of normal (0.6-1.5 mg/dL)
- f) Received IV glutamine less than 4 weeks prior to screening
- g) Receiving growth factors (erythropoietin, granulocyte colony-stimulating factor, granulocyte-macrophage colony stimulating factor, and human growth hormone)
- h) Pregnancy or lactation (women of childbearing age will be excluded if they do not agree to either complete sexual abstinence during the study or if they refuse to use at least two forms of highly effective contraception such as oral contraception, injectable or implantable contraception, vaginal rings, or intrauterine devices (IUD))
- i) Active malignancy or suspicion for gastrointestinal malignancy on CT scan obtained during standard clinical care, if available
- j) Not capable of understanding or not willing to adhere to the study visit schedule and drug administration requirements

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

- k) First degree relative with history of intestinal malignancy (gastric, small intestine, colon)
- l) Personal or first degree relative with history of hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, first degree relative with colon cancer
- m) Positive hemoccult (per rectum) obtained during standard clinical care, if available
- n) Abnormal baseline electrocardiogram (ECG) suggestive of congestive heart failure or underlying cardiac disease
- o) Taking oral benzodiazepines, barbiturates, or phenothiazines

## 5) Procedures Involved

Study team will screen the inpatient census and clinic roster of the “Surgical Nutrition” team at the University of Miami Hospital and identify potentially eligible subjects with enterocutaneous fistulas. If the patient meets all inclusion/exclusion criteria, a member of the study team will then approach the patient or surrogate. Re-screening of patients can be made at the PI’s discretion, if the patient meets all of the inclusion, and none of the exclusion criteria.

### **Eligibility Screening Visit(s):**

Screening procedures can be completed over several visits

Obtain informed consent

Demographics

Medical and surgical history

Review prior and concomitant medications

Collect Physical exam

Collect Vital signs measurements

ECG

Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose) if not done in the last 90 days

Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase) if not done in the last 90 days

Serum pregnancy test if applicable

Collect Concomitant medical review

Collect Nutritional assessment

3-day average fistula output

### **Enrollment within 2 months of signing consent**

Inclusion/Exclusion criteria

Vital signs measurements

Nutritional assessment

3-day average fistula output

Complete questionnaires (see additional documents):

1. ASCQ-Me Short Form v2.0 - Social Functioning Impact
2. ASCQ-Me v2.0 - Sleep Impact Short Form

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

3. Global Health Scale v1.2
4. PROMIS Scale v1.0 - GI Belly Pain
5. PROMIS Scale v1.0 - GI Diarrhea
6. PROMIS Scale v1.0 - GI Nausea and Vomiting
7. PROMIS SF v2.0 - Ability to Participate

Teaching of self-administration of medication

After study enrollment, the subject will be randomly assigned (by a computerized method, using the site 'www.sealedenvelope.com') to begin teduglutide treatment immediately or to continue standard of care (SOC) treatment. The randomization will be performed by a member of the study that is not involved in the informed consent process, and will be enclosed in sequentially numbered opaque envelopes. The envelopes will be given to the PI prior to the enrollment visit. At study visit 5 (day 56), the subject will then cross-over to the opposite treatment assignment. The half-life of teduglutide is 2-3 hours. During the period the subjects are on the "SOC only" treatment arm, the subjects will be given the option to replace some Study visits with Telephone Calls for their convenience. If study visits overlap due to the time window, either visit may be skipped or completed on the same day. Please see information below, and the Study schema.

**Study Visit 1 or Telephone Call as applicable (Day 7) (+/- 3 days)**

Collect physical examination if during visit

Collect Vital Signs measurements if during visit

Monitor severe adverse events (SAE) and adverse events (AE)

Collect concomitant medication review

Collect Nutritional Assessment

3-day average fistula volume (3 days immediately preceding study visit) from the Diaries

Collect adjustment of medications and fluids if recorded

**Study Visit 2 or Telephone Call as applicable (Day 14) (+/- 3 days)**

Collect physical examination if during visit

Collect Vital Signs measurements if during visit

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

3-day average fistula volume (3 days immediately preceding study visit) from the Diaries

Collect adjustment of medications and fluids if recorded

**Telephone Call 1 (Day 21) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)

Nutritional Assessment

3-day average fistula volume (3 days immediately preceding telephone call)

Adjustment of medications and fluids if necessary

**Study Visit 3 (Day 28) (+/- 1 week)**

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Collect physical examination  
Collect Vital Signs measurements  
Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)  
Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase)  
Plasma PK (Pharmacokinetics)

- Processed according to separate “Sample Processing Procedure”

Serum pregnancy test  
Monitor severe adverse events (SAE) and adverse events (AE)  
Collect Concomitant medication review  
Collect Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding study visit)  
Collect adjustment of medications and fluids if recorded

**Telephone Call 2 (Day 35) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)  
Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding telephone call)  
Adjustment of medications and fluids if necessary

**Study Visit 4 or Telephone Call as applicable (Day 42) (+/- 1 week)**

Collect physical examination if during visit  
Collect Vital Signs measurements if during visit  
Monitor severe adverse events (SAE) and adverse events (AE)  
Collect Concomitant medication review  
Collect Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding study visit)  
Collect adjustment of medications and fluids if recorded

**Telephone Call 3 (Day 49) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)  
Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding telephone call)  
Adjustment of medications and fluids if necessary

**Study Visit 5, Cross-over, (Day 56) (+/- 1 week)**

Collect physical examination  
Collect Vital Signs measurements  
Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)  
Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase)

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Plasma PK (Pharmacokinetics)

- Processed according to separate “Sample Processing Procedure”

Serum pregnancy test

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

3-day average fistula volume (3 days immediately preceding study visit)

Collect adjustment of medications and fluids if recorded

Fistula closure (y/n)

Complete Questionnaires (see additional documents)

**Study Visit 6 or Telephone Call as applicable (Day 63) (+/- 1 week)**

Collect physical examination if during visit

Collect Vital Signs measurements if during visit

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

3-day average fistula volume (3 days immediately preceding study visit)

Collect adjustment of medications and fluids if recorded

**Study Visit 7 or Telephone Call as applicable (Day 70) (+/- 1 week)**

Collect physical examination

Collect Vital Signs measurements

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

3-day average fistula volume (3 days immediately preceding study visit)

Collect adjustment of medications and fluids if recorded

**Telephone Call 4 (Day 77) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)

Nutritional Assessment

3-day average fistula volume (3 days immediately preceding telephone call)

Adjustment of medications and fluids if necessary

**Study Visit 8 or Telephone Call as applicable (Day 84) (+/- 1 week)**

Collect physical examination if during visit

Collect Vital Signs measurements if during visit

Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)

Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase)

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- Processed according to separate “Sample Processing Procedure”

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Serum pregnancy test  
Monitor severe adverse events (SAE) and adverse events (AE)  
Collect Concomitant medication review  
Collect Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding study visit)  
Collect adjustment of medications and fluids if recorded

**Telephone Call 5 (Day 91) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)  
Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding telephone call)  
Adjustment of medications and fluids if necessary

**Study Visit 9 or Telephone Call as applicable (Day 98) (+/- 1 week)**

Collect physical examination  
Collect Vital Signs measurements  
Monitor severe adverse events (SAE) and adverse events (AE)  
Collect Concomitant medication review  
Collect Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding study visit)  
Collect adjustment of medications and fluids if recorded

**Telephone Call 6 (Day 105) (+/- 3 days)**

Monitor severe adverse events (SAE) and adverse events (AE)  
Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding telephone call)  
Adjustment of medications and fluids if necessary

**Study Visit 10, End of Treatment (EOT), (Day 112) (+/- 1 week)**

Collect physical examination  
Collect Vital Signs measurements  
Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)  
Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase)  
Plasma PK (Pharmacokinetics)

- Processed according to separate "Sample Processing Procedure"

Serum pregnancy test  
Monitor severe adverse events (SAE) and adverse events (AE)  
Collect Concomitant medication review  
Collect Nutritional Assessment  
3-day average fistula volume (3 days immediately preceding study visit)  
Collect adjustment of medications and fluids if recorded  
Fistula closure (y/n)  
Complete Questionnaires (see additional documents)



IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

**Study Visit 11, Long-Term Follow-up Visit, 3 months after EOT (-2 weeks/+3 months)**

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

Chemistry Panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)

Liver Function tests (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine aminotransferase, aspartate aminotransferase, lipase, amylase)

Plasma PK (Pharmacokinetics)

- Processed according to separate "Sample Processing Procedure"

3-day average fistula volume (3 days immediately preceding study visit)

Fistula closure (y/n)

Complete Questionnaires (see additional documents)

**Open-Label Extension Study Visit (up to 12 additional visits) to occur monthly (+/- 1 week)**

**\*Visits may be conducted virtually due to the Covid-19 outbreak.**

Collect physical examination results

Collect Vital Signs measurement results

Collect most recent Chemistry Panel results approximately every 3 months (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine glucose)

Collect Liver Function test results approximately every 3 months (total bilirubin, direct bilirubin, alkalkine phosphatase, alanine

aminotransferase, aspartate aminotransferase, lipase, amylase)

Collect Serum pregnancy test results every 3 months if completed

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medications

Collect Nutritional Assessment if completed

Collect approximate daily average fistula volume

Collect adjustment of medications and fluids if recorded

**Open-Label Extension Telephone Visit to occur every 2 weeks (+/- 3 days) alternating with Open-Label Extension Study Visits**

Monitor severe adverse events (SAE) and adverse events (AE)

Collect Concomitant medication review

Collect Nutritional Assessment

Collect approximate daily average fistula volume

Collect adjustment of medications and fluids if recorded

**Drug Administration, Dispensation and Disposition**

Once consent is obtained and necessary baseline data collected, the subject will begin receiving teduglutide (0.05 mg/kg/d, for moderate renal impairment defined as serum

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

creatinine > 1.5 times the upper limit of normal, the dose will be reduced to 0.025 mg/kg/d, administered once daily subcutaneously into the abdomen, thigh, or arm (at approximately the same time each day) for 8 weeks. For enrolled subjects demonstrating a favorable trend and are deemed to be reliable (both as determined by the PI) but still have a fistula at the end of treatment (EOT) or long-term follow-up, the subject will be offered an “open-label” extension whereby they will continue to receive teduglutide at the previous dose for up to another 12 months or permanent fistula closure, whichever occurs first.

Immediately prior to initiating the 8-week period of drug administration, the subject will receive training on how to safely reconstitute and administer the medication. The volume of reconstituted study drug to be administered is a fixed dose of 0.005 mL/kg body weight. Each day, the injection site should be changed. 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. Dates of days with missed or incomplete doses are to be reported in the diary. The subject is going to be instructed to bring back all used and unused IP. The IP will then be disposed of per pharmacy SOP. University of Miami Research Pharmacy will be receiving, storing, dispensing, keeping inventory, and disposing the IP for this study as per their standard operating procedures.

Study drug will be packaged, labeled, and delivered to the clinical center by the sponsor or designee. Each study drug kit will contain labeling with the general dosage instructions, storage conditions, expiration date, kit number, and company name. 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 (GMP). Ancillary supply kits containing syringes with needles for injection and reconstitution, sterile water, and alcohol swabs will also be provided.

The Principle Investigator or designee will conduct an inventory upon receipt of the clinical supplies and will acknowledge receipt of the supplies to the sponsor. A copy of the shipping documents will be maintained for records. Study drug will be kept at controlled room temperature (15°-25°C, 59°-77°F) in a secure location until dispensed to the subject. Subjects will be instructed to keep study drug at controlled room temperature. The sterile water diluent should be stored at controlled temperature.

Study drug kits will be dispensed to subjects at each of the office visits during the 8 weeks of dosing and up to an additional 52 weeks of “open-label” extension at which the subject is required to be at the clinic. Each study drug kit is sufficient for a treatment period of 4 weeks (depending on visit #). The PI will 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 will be accounted for and in no case will clinical supplies be used in an unauthorized situation.

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Subject compliance will be checked at every visit (and telephone call) by asking the subjects if they have taken their study drug according to instructions and by reviewing the subject diary if available and to perform drug accountability. Compliance is considered to be achieved if the subject reports (by diary or discussion) 80% of the planned doses administered. The hierarchy of source documentation is the Diary as primary, and if not available then followed by study staff documentation of weekly visits and lastly documentation of monthly visits.

At present, the standard of care (SOC) for ECF involves source control treatment of intra-abdominal infection, nutritional support via enteral nutrition (EN), parenteral nutrition (PN), or oral intake, careful fluid and electrolyte management, and occasionally surgical repair. Subjects enrolled in this study will still receive SOC in addition to 8 weeks of teduglutide therapy and up to an additional 52 weeks of open-label extension when this applies.

Unless contraindicated by clinical condition, enrolled patients will undergo colonoscopy within 6 months prior to starting the drug.

#### **6) Data and Specimen Banking\***

All subjects will undergo laboratory assessment (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, lipase, amylase) before starting teduglutide and subsequent laboratory tests will be performed as stated in the schedule below. These labs are normally drawn during the course of clinical care.

Specifically, the labs which will be assessed in this study are:

Total bilirubin ( normal 0.0 – 1.0 mg/dL)

Alkaline phosphatase (normal 45 -115 U/L)

Lipase (normal 13 – 60 U/L)

Creatinine (normal 0.6-1.5 mg/dL)

#### **Data Fields**

Age

BMI

Gender

Charlson Comorbidity Index

Questionnaires (see additional documents)

Cause of major intestinal resection: trauma, emergency operation, elective operation, inflammatory bowel disease, other

Location of fistula: stomach, duodenum, jejunum, ileum, colon

Days since last operation

Days since fistula diagnosis

Type of nutrition: per os (PO), enteral nutrition (EN), parenteral nutrition (PN), PO + EN, PO + TPN, EN + PN, PO +EN + PN

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Concomitant medications: antidiarrheals, antisecretory agents  
3-day average fistula volume (continuous variable)  
Output of fistula >500 mL/day (Y/N)

Because of the expected increase in luminal absorption, subjects will be closely monitored for increased oral medication absorption, particularly opioids and sedating medications. Subjects will be assessed for pinpoint pupils and lethargy. If clinical evidence of increased oral medical absorption is discovered, the doses will be accordingly decreased. If clinical evidence of fluid overload is discovered (such as breathlessness, subjective dyspnea, new-onset pitting peripheral edema, change in body weight, jugular venous distention, and rales on lung auscultation), then EN and PN prescription will be decreased accordingly.

Additionally, subjects will be monitored for clinical evidence of volume depletion. Clinical signs suggestive of volume depletion include dry mucus membranes, poor skin turgor, decreased urine output, or rapid body weight loss.

Fluid and volume status will be assessed according to the usual clinical signs and symptoms: breathlessness, subjective dyspnea, new-onset pitting edema, change in body weight, and rales on lung auscultation. This will be assessed both in person at the time of study visit as well as by self report from the subject during phone calls.

Criteria for discontinuation of teduglutide in patients who experience fluid overload include: decrease in room-air oxygen saturation > 5% from baseline, significant worsening of peripheral edema resulting in functional limitation, severe dyspnea resulting in functional limitation, and hospitalization for congestive heart failure.

Data will be de-identified and stored on password-protected network accessible only to research staff. Data will be retained for at least six years following conclusion of the study on this network.

## **7) Biostatistical Analysis**

Because this is a pilot study enrolling only 10 subjects, no sample size or power calculation was performed. The primary endpoint (decrease in fistula volume by 20%) was chosen based on previous studies in a different population.

Continuous outcome variables that are normally distributed will be presented as mean  $\pm$  Standard Deviation (SD) while continuous outcome variables that are not normally distributed will be presented as median and interquartile range (IQR). In calculating the difference in fistula volume between baseline and final measures, a two-sample t-test for independent samples will be used. A p value of <0.05 will be considered significant.

## **8) Risks to Subjects\***

Because of its intestinotrophic mechanism of action, teduglutide may theoretically increase the risk of neoplastic growth, though this has never been proven in clinical trials. For this

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

reason, patients with evidence or suspicion of active gastrointestinal malignancy will not be enrolled. Abdominal computed tomography scans obtained during the course of routine clinical care will be reviewed for evidence of gastrointestinal malignancy and any patients with concerning findings (as described by the final Radiologist's interpretation) will be excluded. Additionally, patients with a familial history of intestinal malignancy (gastric, small intestine, colon) will be excluded.

For patients meeting American College of Gastroenterology (ACG) colon cancer screening criteria based on age (age 50, or age 45 years in African Americans) who have not had a negative colonoscopy in the 5 years preceding study enrollment, a screening **CT colonography** will be offered. All enrolled patients will be advised of the potential for acceleration of neoplastic growth included in the Gattex (teduglutide) label's Warnings and Precautions, as well as the recommendation for colonoscopy with removal of polyps prior to initiating treatment with Gattex. CT colonography will be offered as an alternative method of screening. Patients with abnormal findings concerning for malignancy will be excluded.

Additional possible safety risks with teduglutide identified in the previous trials also include gastrointestinal obstruction; gallbladder, biliary tract, and pancreatic disease; increased absorption of fluids leading to fluid overload in patients with cardiovascular disease; and increased absorption of oral medications with narrow therapeutic index.

**The grades of adverse events described below are taken from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.3.0.**

Intestinal obstruction occurred in 3.9% (n=6) of patients receiving teduglutide in the prior studies, with an onset between 6 days and 19 months. Only 1 patient required surgical intervention. Subjects will be monitored clinically for signs and symptoms of GI obstruction. For those patients who develop obstruction, teduglutide will be temporarily discontinued while the patient is clinically managed and restarted when the obstructive presentation resolves, if clinically indicated.

Biliary symptoms of cholecystitis and gallstones/sludge occurred in 7.5% (n=13) of patients in previous teduglutide studies, though almost half of them had a history of biliary disease prior to enrollment. None of the biliary events necessitated study withdrawal.

Pancreatitis developed in 1.7% (n=3) of all teduglutide-treated patients in previous trials, though all three patients had a history of pancreatitis prior to enrollment. None of the events required study withdrawal.

Fluid overload developed in 13.3 % (n=23) of all teduglutide-treated patients in pooled Phase III studies. Subjects will be closely monitored for increased oral medication absorption, particularly opioids and sedating medications. Subjects will be assessed for pinpoint pupils and lethargy. If clinical evidence of increased oral medical absorption is

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

discovered, the doses will be accordingly decreased. If clinical evidence of fluid overload is discovered (such as breathlessness, subjective dyspnea, new-onset pitting peripheral edema, change in body weight, and rales on lung auscultation), then EN and PN prescription will be decreased accordingly.

During weekly assessments, if the patient is on PN and there are clinical signs or suspicion of fluid overload, the PN volume will be decreased by 10% to 30% in coordination with the PN Pharmacy. We will then continue monitoring and adjust PN/IV volume accordingly to maintain clinical nutrition and volume status.

Criteria for discontinuation of teduglutide in patients who experience fluid overload include: decrease in room-air oxygen saturation > 5% from baseline, significant worsening of peripheral edema resulting in functional limitation, severe dyspnea resulting in functional limitation, and hospitalization for congestive heart failure.

Because of the laboratory safety monitoring, the subjects will require blood draws before teduglutide initiation, at the mid-point of treatment (week 4), after the completion of the 8 week trial, and at long-term follow up (3 months after end of treatment). Patients with persistently abnormal laboratory results and ongoing adverse reactions will be followed until resolution and will undergo repeat laboratory testing as necessary to ensure resolution of all abnormal laboratory results potentially attributable to study drug. For patients receiving parenteral nutrition, this will not impact them as they will be getting test performed as part of routine care. However, for patients not requiring parenteral nutrition, this entails additional minimal blood loss and the discomfort of needle stick.

The most common adverse events identified in the previous trial (Jeppesen 2012, Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure) are mild and related to gastrointestinal symptoms such as abdominal pain (31%), nausea (29%), and abdominal distension (21%).

### **9) Adverse Event (AE) 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 temporarily 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
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

- 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.

Although an overdose of the study drug or concomitant medication without any clinical sign or symptom is not technically an AE, it will be captured as an AE to provide valuable safety data on higher untested doses of study drug.

### **Procedures for Reporting Adverse Events**

Adverse events may be spontaneously reported, obtained through non-leading questioning, or noted during examination of a subject. Adverse events will be recorded from the signing of informed consent through the last dose of study drug. Serious adverse events will be recorded from the signing of informed consent through 30 days after the last dose of study drug.

At each visit, new AEs are recorded sequentially on the Adverse Event log. The AE term will note the diagnosis whenever possible, not the individual signs or symptoms (eg., myocardial infarction will be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECT). Also recorded are:

- Start and stop date and time
- Whether or not 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 (i.e. the relationship cannot be ruled out).
- Whether or not the AE is serious (i.e. an SAE). If identified as an SAE, the AE will be reported as an SAE.
- Actions taken (none, study drug dose interrupted, study drug discontinued, other medication change, non-drug therapy, change in parenteral nutrition or IV fluids).
- Outcome (resolved, severity or frequency increased, ongoing, fatal). An individual AE receives only one outcome.

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

Adverse events not resolved at the end of treatment will be followed until resolution or until the AE is judged by the investigator to have stabilized.

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

- Are considered clinically significant by the investigator
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study

### **Serious Adverse Events**

An event that is serious will be recorded on the Serious Adverse Event log. SAEs will be recorded from the signing of informed consent through 30 days after the last dose of study drug.

The most common adverse events are mild and related to gastrointestinal symptoms such as abdominal pain, nausea, and vomiting. If these occur, they will be noted in the adverse event tracking log and reported to the IRB during Continuing Review.

More serious adverse events and any unexpected adverse events will be recorded as per UM HSRO policies and procedures.

### **Events Necessitating Withdrawal from Study**

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:
  - Significant, active, uncontrolled cardiac, hepatic, or renal dysfunction as defined by the Inclusion/Exclusion criteria
- New diagnosis of inflammatory bowel disease
- Use of any excluded medication
- Pregnancy
- 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
- Principal Investigator decision (i.e. subject non-compliance with study procedures)
- Significant AE or medical decision that precludes the subject from adhering to study requirements

Readmission to the hospital for fistula-related complications (ex: cellulitis, intra-abdominal abscess, dehydration, etc.) is common and is likely to occur during the study treatment and follow-up period. Unless one of the above “Events Necessitating Withdrawal” occurs, the subject will remain enrolled in the study during hospitalization.



IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

### **10) Potential Benefits to Subjects**

Based on the encouraging results in studies of teduglutide for patients with short bowel syndrome, we expect a clinically significant decrease in daily ECF volume of about 20% magnitude. This could convert high-output fistulas (>500 mL/day) to medium- (200-500 mL/day) or low-output fistulas (<200 mL/day), significantly simplifying fluid/electrolyte management, allow for liberation from parenteral nutrition, or even resolve low-output fistulas completely. It is reasonable to expect an improvement in quality of life.

### **11) Vulnerable Populations\***

We will not routinely enroll pregnant women, prisoners, children, or cognitively impaired adults.

### **12) Resources Available**

The PI has many years of experience conducting and being trained for clinical research. All study personnel will be trained on the protocol by the investigator or designee and complete CITI training. Those obtaining consent will also have prior experience communicating with patients.

### **13) Prior Approvals**

None

### **14) Recruitment Methods**

#### **Recruitment Procedures**

The Study Staff will perform a daily screen of the inpatient census of the “Surgical Nutrition” team at the University of Miami Hospital as well as the outpatient census of the Surgical Nutrition clinic for adults with ECF. In order to screen for eligible patients, the study team is requesting partial HIPAA waiver. When a patient is found to be eligible, the primary health provider team (usually a physician or nurse practitioner) who is known to the potential subject will be contacted for approval for the patient to be contacted for research purposes. This provider will initially introduce the study to the patient and verbally obtain the patient’s permission to be contacted by study staff. The patient will then be approached for discussion of the trial and informed consent, as outlined in the consent procedures below.

Potential subjects will not be contacted by phone for recruitment. Recruitment will not involve restrictions on sociodemographic factors including gender or ethnic characteristics. Recruitment will be devoid of any procedures which could be construed as coercive. If the potential subject is the Investigator’s own patient, the Investigator will ask a physician colleague to initially explain the study and also recommend that the patient discuss participation with other health care providers. These colleagues will stress that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future.

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

**15) Local Number of Subjects: 10**

**16) Monitoring And Quality Assurance**

Study Staff will maintain the data in an electronic database stored in a secure location on password-protected computer system. The consent forms will be kept in files which will be stored in a secure location. De-identified data will be uploaded to VELOS electronic database. The PI will confirm the completeness of data being entered in the electronic database

In order to protect all subjects' confidentiality, we will store data on a password-protected network. Subjects will receive a study-specific unique identifier and the medical record number (MRN) will be uncoupled from the data. The decoder key for study identifier and MRN will be stored in a separate, password-protected file.

**Trial Monitoring, Auditing, and Inspecting**

The investigator will permit trial-related monitoring, quality audits, and inspections by, government regulatory authorities, of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities.

In addition to the Clinical Monitoring component of this protocol, Quality Assurance (QA) to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

**17) Confidentiality**

The protected health information collected for the purpose of this research study will be assigned a research code number and any obvious patient identifiers (name, social security number, hospital record number) will be removed from this information. Both the confidential health information and the information linking the research code numbers to the patients' identities will be stored in a secure manner (e.g., locked file cabinet, password protected database) accessible only to the research study personnel. The information linking the research code numbers to the patients' identities will be stored separate from the confidential health information.

Clinical data will be collected for no longer than one year after the patient has had the initial surgery. Data will be de-identified and stored on a password-protected network

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

accessible only to research staff. Data will be retained for at least six years following conclusion of the study on this network.

### **18) Provisions to Protect the Privacy Interests of Subjects**

Access to patients and their protected health information along with the collection and analysis is necessary in order to conduct this research study. Consistent with the “minimum necessary standard” of the HIPAA privacy rule, we will only access and collect the specific health information necessary to complete this research study.

Some of the research investigators who will access and use the protected health information may also be involved directly in the care of the respective patients, thus obviating the privacy and confidentiality concerns.

Authorization to obtain protected health information will be obtained from the patient or their proxy as soon as possible. It is nearly impossible to provide authorization during a crisis situation in critical care areas during the workup of a critically ill patient. Generally, these patients are intubated, sedated, and hemodynamically compromised, especially during the initial days after admission.

The protected health information collected for the purpose of this research study will be assigned a research code number and any obvious patient identifiers (name, social security number, etc) will be removed from this information. Both the confidential health information and the information linking the research code numbers to the patients’ identities will be stored in a secure manner (e.g., locked file cabinet, password protected database) accessible only to the research study personnel.

### **19) Consent Process**

#### **19a. Remote Consenting will include the following:**

- Send a copy of the consent document via secure email or U.S. Mail.
- Arrange for a witness to attend and witness the consent discussion.
- Let the participant know that a witness will join the consent meeting.
- Set up a video meeting or 3-way call and send an invitation to the attendees.

We will ask the participant to scan or take a picture of each page of the documents and email the signed/dated documents to the study team. As an alternative, we may establish a secure network location for uploading the consent document.

During meeting:

- Identify everyone on the call.
- Review the informed consent with the participant, answer the participant’s questions and ask questions of the participant to confirm comprehension.
- Ask the participant if s/he consents to participate/continue participation.
- If the participant agrees, ask him/her to sign and date the consent document.
- If using 3-way call, ask the participant to confirm s/he signed & dated the document.

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

We will ask the participant to scan or take a picture of each page of the documents and email the signed/dated documents to the study team. As an alternative, the research could establish a "UM Box" location for uploading the consent document.

If the person is unable to take a picture, we will document the circumstances.

The person conducting the consent process will sign and date a copy of the consent document.

The witness will sign & date on the witness line of a copy of the consent document.

The person conducting the consent process will document the purpose for the remote consent (COVID-19), and each step of the process. The note will explain why the research team doesn't have the signed and dated document.

Documenting the Remote Consent process

The originals of the informed consent document signed by the investigator (and possibly the witness) will be placed in the participant's research record.

The person obtaining consent will document how s/he confirmed that the patient consented and signed the consent form. The note will include a statement indicating why the informed consent document signed by the participant was not retained, (e.g., due to contamination of the document by infectious material.)

If the participant cannot send a picture of the signed document, the person obtaining consent will document why a copy of the signed document is not available. See example below.

Example:

Informed consent was obtained on Date at Time. The participant could not come to the site for the consent process due to COVID-19 social distancing requirements. A copy of the consent document was emailed to the prospective participant before the consent discussion

The consent process was performed by phone/ZOOM. The individuals attending the discussion were: (list the names of the individuals). The person obtaining consent explained the research to the participant and answered the participant's questions. The person obtaining consent asked the participant questions to ascertain whether the s/he understood the study, and the participant was able to answer the questions. The participant voluntarily agreed to participate. The subject/LAR signed and dated the consent document. The research was not able to obtain a copy of the signed original

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

consent document because consent was obtained remotely, and the document may transmit the COVID-19 infection.

After signing the consent document, the participant took a picture and sent it to the research team/ OR The participant was unable to send a picture of the document. A witness observed the entire process.

The consentor will then add similar documentation about the HIPAA authorization.

**19b. In person consenting:**

The patient will be approached in the clinic area by a member of the research staff. Any of the staff members listed on the protocol will discuss the risks and benefits of participation. If the staff member is not fluent in the patient's native language, they will use a translator to obtain informed consent in a document written in the patient's native language. Initiating this process may also occur over the phone and during scheduling and may include mailing of the consent form to allow for more time to read and understand prior to coming into clinic.

Subject/Proxy will be given an ICF in their native language (English/Spanish only). They will be given ample time to review the ICF with family, clergy, friends or primary physicians. Once they have agreed they will be required to sign ICF before any study procedures can be done on the subject. A copy of the ICF will be given to the subject/proxy and one will be placed in the medical records. The original will stay in the subject's source documentation folder located in the Trauma Research Office.

Patients who are incapacitated or unable to sign their own consent will not be enrolled in the study, as compliance is less likely and compromise the study.

**Non-English Speaking Subjects**

A translated written informed consent document will be provided in a language understandable to the participant. This will be an accurate translation of the IRB-approved English version of the full informed consent document.

**20) Process to Document Consent in Writing**

We will document consent with a translated written informed consent document in a language understandable to the participant. If subjects who do not speak English are eligible, we ensure that the oral and written information provided to those subjects will be in that language either by research personnel fluent in that language or by an institutional translator. We will pursue approval of the consent documents in Spanish as a significant portion of the subject population may speak Spanish. We also request permission to utilize the short forms for documentation of consent and translation into other than the English or Spanish for the rare circumstance that the subject or proxy cannot communicate in either of those languages.

IRB Study Number: 20170189

NCT02889393

Version Date: June 16, 2021

PI: Daniel Dante Yeh, MD

**21) Publication policy/ Results Reporting/Progress and Final Reports**

ClinicalTrials.gov requirements (registration/results publication)

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 years after the completion of the primary endpoint by contacting the PI

IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

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IRB Study Number: 20170189  
Version Date: June 16, 2021  
PI: Daniel Dante Yeh, MD

NCT02889393

## **Appendix B**

## **Appendix C**

### **MEDICATION GUIDE FOR PATIENTS**



Medication Guide for  
patients.pdf



IRB Study Number: 20170189  
 Version Date: June 16, 2021  
 PI: Daniel Dante Yeh, MD

NCT02889393

## Appendix D

### Charlson Comorbidity Index

**Table 1. Charlson Comorbidity Index Scoring System**

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm $\geq 6$ cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumor without metastases (exclude if $>5$ y from diagnosis) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)

NOTE. For each decade  $> 40$  years of age, a score of 1 is added to the above score.

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

IRB Study Number: 20170189  
 Version Date: June 16, 2021  
 PI: Daniel Dante Yeh, MD

NCT02889393

**Appendix E Treatment Schema**

	Eligibility / Screening	Enrollment	Treatment							Cross-over
			Day 7 Study Visit 1 +/- 3 days	Day 14 Study Visit 2 or Telephone +/- 3 days	Day 21 Telephone Call 1 +/- 3 d	Day 28 Study Visit 3 +/- 1 week	Day 35 Telephone Call 2 +/- 3 days	Day 42 Study Visit 4 or Telephone +/- 1 week	Day 49 Telephone Call 3 +/- 3 d	Day 56 Study Visit 5 +/- 1 week
Informed Consent	X	X								
Inclusion and exclusion criteria	X	X								
Demographics	X									
Medical and surgical history	X									
Review prior and concomitant medications	X									
Complete Physical Exam <sup>A</sup>	X		X	X		X		X		X
Vital signs measurements <sup>B</sup>	X	X	X	X		X		X		X
Self-administration of medication and teaching if needed		X	X	X	X	X	X	X	X	X
IP Dispensation and Accountability		X	X	X		X		X		X
Chemistry panel	X					X				X
Liver function tests	X					X				X
Plasma PK*						X				X
Serum pregnancy test	X					X				X
ECG	X									
Monitor SAE/AE <sup>C</sup>			X	X	X	X	X	X	X	X
Concomitant medication review	X		X	X		X		X		x
Nutritional assessment <sup>D</sup>	X	X	X	X	X	X	X	X	X	X
3- day fistula output	X	X	X	X	X	X	X	X	X	X
Questionnaires		X								X

IRB Study Number: 20170189  
 Version Date: June 16, 2021  
 PI: Daniel Dante Yeh, MD

NCT02889393

	Treatment							End-of-Treatment	Long-Term Follow-up
	Day 63 Study Visit 6 or Telephone +/- 1 week	Day 70 Study Visit 7 or Telephone +/- 1 week	Day 77 Telephone Call 4 ± 3 d	Day 84 Study Visit 8 ± 1 week	Day 91 Telephone Call 5 ± 3 d	Day 98 Study Visit 9 or Telephone +/- 1 week	Day 105 Telephone Call 6 ± 3 d	Day 112 Study Visit 10 ±1 week	Study Visit 11 (3 months after EOT) -2wks to +3 mos.
Informed Consent									
Inclusion and exclusion criteria									
Demographics									
Medical and surgical history									
Review prior and concomitant medications									
Complete Physical Exam <sup>A</sup>	X	X		X		X		X	
Vital signs measurements <sup>B</sup>	X	X		X		X		X	
Self-administration of medication and teaching if needed	X	X	X	X	X	X	X		
IP Dispensation and Accountability	X	X		X		X		X <sup>E</sup>	
Chemistry panel				X				X	X
Liver function tests				X				X	X
Plasma PK*				X				X	X
Serum pregnancy test				X				X	X
Monitor SAE/AE <sup>C</sup>	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X		X		X		X	X
Nutritional assessment <sup>D</sup>	X	X	X	X	X	X	X	X	X
3- day fistula output	X	X	X	X	X	X	X	X	X
Questionnaires								X	X

IRB Study Number: 20170189  
 Version Date: June 16, 2021  
 PI: Daniel Dante Yeh, MD

NCT02889393

	<b>Open-Label Extension (up to 12 additional Study Visits and 12 additional Telephone Calls)</b>		
	Extension Study Visit 1 +/- 1 week	Extension Study Telephone Call 1 to End ± 4 d	Extension Study Visit 2 to End +/- 1 week
Informed Consent	X		
Collect Complete Physical Exam Results <sup>A</sup>	X		X
Collect vital signs measurements <sup>B</sup>	X		X
Self-administration of medication and teaching if needed	X	X	X
IP Dispensation and Accountability	X		X
Collect chemistry panel results <sup>**</sup>	X		X
Collect liver function test results <sup>**</sup>	X		X
Collect serum pregnancy test (if applicable)	X		X
Monitor SAE/AE <sup>C</sup>	X	X	X
Collect concomitant medication review	X	X	X
Nutritional assessment <sup>D</sup>	X	X	X
Approx. average daily fistula output	X	X	X
Questionnaires			X <sup>F</sup>

A. A complete physical examination during an applicable study visit will include an assessment as per clinical judgement.

B. Vital sign measurements during an applicable study visit will include body temperature, heart rate, respiratory rate, and blood pressure. Height will be obtained at Screening only; weight will be measured at screening and during applicable study visits.

C. Patients will be monitored for non-serious adverse events and serious adverse events from the time when informed consent is obtained at Screening up to and including 30 days for SAEs and through the Long Term Follow Up (Study Visit 11) for AEs.

D. May include adjustment of parenteral nutrition (PN) volume as per pre-defined weaning protocol.

E. IP accountability only at visit 10

F. Questionnaires for the Open-Label Extension Study will only be administered at the End of the study

\* PK = Pharmacokinetics, processed according to separate "Sample Processing Procedure"

\*\* Laboratory test results for the Open-Label Extension Study may be collected every 3 months if completed clinically