Quotient Sciences

CLINICAL STUDY PROTOCOL

A Pharmacokinetic Study of PLENVU® in Healthy Subjects

Quotient Study Number:	QCL117983
Sponsor Study Number:	NER1006-03/2016 (PKPU)
EudraCT Number:	2017-003440-20
Clinical Trials gov Identifier	NCT03437265
IND Number:	120089

Clinical Study Site:

Quotient Sciences
Mere Way
Ruddington Fields
Ruddington, Nottingham
NG11 6JS
United Kingdom
Tel: +44 (0)115 974 9000

Sponsor:

Norgine Ltd.
Norgine House, Widewater Place
Moorhall Road
Harefield, Uxbridge
UB9 6NS
United Kingdom
Tel. +44 (0)1895 826600

Date of Protocol: 19 May 2020

Status of Protocol: Version 4.0

SPONSOR/QUOTIENT SCIENCES CONFIDENTIAL

Study Contacts

Principal Investigator:
Philip Evans MBChB, MRCS (Ed)
Quotient Sciences
Mere Way
Ruddington Fields
Ruddington
Nottingham
NG11 6JS
United Kingdom

Tel: +44 (0)115 974 9000 (day)
Tel: +44 (0)7774 017236 (out of hours emergency)

Sub-Investigators:
Sharan Sidhu MBChB, BAO, MRCS
Stuart Mair MBChB, DRCOG, DCPSA, MFPM
Nand Singh BSc, MD, DPM, MFPM
Litza McKenzie MBChB, BScMedSci
Martina Fieldingova MUDr
Elizabeth Maria van Niekerk MBChB, DipPalMed
Somasekhara Menakuru MBBS, MS, MRCS, DPM
Jonathan Whitton BMBS, BSc, MRCS, PGcert
David Everton BSc, MBBS
Conor Clerkin-Oliver MBChB, MSc
Quotient Sciences

Tel: +44 (0)115 974 9000 (day)
Tel: +44 (0)7774 017236 (out of hours emergency)

Quotient Project Manager:
Lauren Shurety
Quotient Sciences

Tel: +44 (0)115 931 5530

Study Monitor:
Jane Muir
Wirral Clinical Consultancy Ltd.
76 Pipers Lane
Heswall
Wirral,
Merseyside
CH60 9HN
United Kingdom

Medical Monitor:	Richard Ng Kwet Shing (Office Hours) Director, Clinical Development Norgine Ltd Norgine House, Widewater Place Moorhall Road, Harefield, Uxbridge UB9 6NS United Kingdom Tel: +44 (0)1985 453 584 Tel: +44 (0)7590 976646 ProPharma Group (Out of Hours) Olliver, Aske, Richmond North Yorkshire, DL10 5HX Tel: +44 (0)1748 828787
Sponsor's Representative:	Lucy Clayton Therapy Area Director, Clinical Development Norgine Ltd Norgine House, Widewater Place Moorhall Road, Harefield, Uxbridge UB9 6NS United Kingdom Tel: +44 (0)1985 826 669
Sponsor's Clinical Project Manager:	Jeff Pilot Norgine Ltd Norgine House, Widewater Place Moorhall Road, Harefield, Uxbridge UB9 6NS United Kingdom Tel: +44 (0)1985 453 736
Pharmacovigilance:	Sheela Ankolekar SEC Associate Director/Senior Safety Physician, Global Pharmacovigilance Norgine Ltd Norgine House, Widewater Place Moorhall Road, Harefield, Uxbridge UB9 6NS United Kingdom Fax: 01895 453732 Email: NORGINE-India@PAREXEL.com

Central Laboratory:	The Doctors Laboratory The Halo Building 1 Mabledon Place London WC1H 9AX United Kingdom
Bioanalytical Laboratory (Glycolic Acid; Ethylene Glycol and Diethylene Glycol for exploratory analysis):	Unilabs - York Bioanalytical Solutions Ltd. Cedar House Northminister Business Park Northfield Lane Upper Poppleton York, North Yorkshire YO26 6QR United Kingdom
Bioanalytical Laboratory (PEG 3350, Ascorbate and Oxalic acid):	Covance Laboratories Limited Otley Road Harrogate, North Yorkshire HG3 1PY United Kingdom
Bioanalytical Laboratory (Ethylene Glycol and Diethylene Glycol for primary analysis)	Charles River Laboratories Den Bosch BV Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

Signatures for Quotient

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the SmPC, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 16.3 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

Philip Evans MBChB, MRCS (Ed)
Principal Investigator
Senior Clinical Research Physician

Signature

20 MAY 2020

Date

Signatures for Sponsor

Lucy Clayton Sponsor's Representative	electronic signature (see next page) Signature Date
Richard Ng Kwet Shing Sponsor's Medical Representative	electronic signature (see next page) Signature Date

Signature Page for TMF-00826 v1.0

Reason for signing: Approved	Name: Richard Ng Role: Clinical Operations Date of signature: 19-May-2020 15:58:45 GMT+0000

Reason for signing: Approved	Name: Lucy Clayton Role: Project Management Date of signature: 19-May-2020 16:45:47 GMT+0000

Signature Page for TMF-00826 v1.0

1 Table of Contents

2 List of Tables and Figures

2.1 Table of In-Text Tables

2.2 Table of In-Text Figures

3 Synopsis

Sponsor: Norgine Ltd.	**Investigational Medicinal Product:** PLENVU® Powder for Oral Solution	**EudraCT No.:** 2017-003440-20 **IND No.:** 120089
Title of Study: A Pharmacokinetic Study of PLENVU® in Healthy Subjects		
Principal Investigator: P Evans MBChB, MRCS (Ed)		
Study Centre: Quotient Sciences, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, United Kingdom		
Rationale: The purpose of this study is to determine if there is systemic exposure to components of the PLENVU (NER1006) formulation. If so, the plasma pharmacokinetic (PK) profiles for the components of PLENVU and their potential metabolites will be determined. In addition, this study aims to provide PK, safety and tolerability results to support the design of paediatric studies for PLENVU.		
Objectives: The primary objective is to characterise the pharmacokinetic (PK) profile of active ingredients of PLENVU®, PEG 3350, ascorbate and potential related substances/metabolites (oxalic acid and glycolic acid using high performance liquid chromatography-mass spectrometry [HPLC-MS], and ethylene glycol and diethylene glycol using gas chromatography-mass spectrometry [GC-MS]). The secondary objectives include the safety, tolerability and pharmacodynamics (PD) characterisation of PLENVU (1-Day Morning Only-Dosing) in healthy adult subjects. The exploratory objective of the study is to measure plasma concentrations of ethylene glycol and diethylene glycol using HPLC-MS.		
Methodology: This is a single centre, open-label, non-randomised, study in healthy adult male and non-pregnant, non-lactating female subjects to investigate the PK of PLENVU as a powder for oral solution formulation (PLENVU Dose 1 and PLENVU Dose 2). It is planned to enrol up to 18 subjects to ensure 12 evaluable subjects complete the study. Subjects will receive PLENVU on Day 1, with at least a 2 h period between the start of each dose. All subjects will receive the powder for oral solution formulations in the same order, i.e. PLENVU Dose 1, containing PEG 3350, sodium sulfate and electrolytes, followed by PLENVU Dose 2, containing sodium ascorbate, PEG 3350, ascorbic acid and electrolytes. **Study Design:** Subjects will be screened for inclusion in the study up to 28 days before dosing. Eligible subjects will be admitted in the afternoon (approximately 16:00) on the day before dosing (Day -1). Subjects will receive a standardised evening meal. At approximately 08:00 on Day 1, subjects will receive PLENVU Dose 1, reconstituted with water and made up to 16 US fl oz (473 mL), and 473 mL of additional water, both to be consumed over a period of 60 min after the start of Dose 1. Dose 2 will be administered at least 2 h after the start of Dose 1. At approximately 10:00, PLENVU Dose 2, reconstituted with water and made up to 16 US fl oz (473 mL), and 473 mL of additional water will be administered in the same manner as PLENVU Dose 1, and both to be consumed over a period of 60 min after the start of Dose 2. Additional water may be drunk *ad libitum* during and after each dose. Blood samples will be		

taken at 1 and 2 h after the end of the evening meal on Day -1, 1 h before Dose 1 and serially from Dose 1 until 60 h after the start of dosing of PLENVU Dose 1, and safety assessments will be performed throughout the study. Subjects will be discharged from the clinic at 60 h after the start of dosing for PLENVU Dose 1, following completion of the PK and safety assessments. There will be a follow-up call 5 to 7 days after dosing to ensure the ongoing wellbeing of subjects.

Number of Subjects Planned:

It is planned to enrol a total of 18 subjects to ensure 12 evaluable subjects complete the study. A subject is considered evaluable if they have received 100% of each dose of PLENVU (i.e. Dose 1 and Dose 2), and 100% of the mandatory 473 mL additional water after each dose, have not vomited post-dose, and have sufficient PK, PD and safety data to meet the objectives of the study.

Subjects withdrawn due to an investigational medicinal product (IMP)-related adverse event (AE), with the exception of IMP-related vomiting, or termination of the study will not be replaced.

Subjects who are withdrawn for other reasons may be replaced at the discretion of the investigator and sponsor to ensure sufficient evaluable subjects. Up to 2 replacement subjects may be enrolled into the study. The maximum number of subjects that may be dosed is 20.

Duration of Study:

The estimated duration of the study is approximately 5 weeks.

Main Inclusion Criteria:

Healthy males and non-pregnant, non-lactating females aged 18 to 30 years.

Body mass index 18.0 to 35.0 kg/m^2.

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMP will be used in this clinical study:

Investigational Medicinal Product	Dose and Route of Administration
PLENVU Powder for Oral Solution	Dose 1: Oral administration of 1 sachet (115.96 g) PLENVU Dose 1 (containing PEG 3350, sodium sulfate and electrolytes), to be reconstituted with water and made up to 473 mL, and 473 mL of additional water to be consumed; both to be consumed over a period of 60 min after the start of Dose 1. Additional water may be drunk *ad libitum* during and after the dose.
	Rest period: Dose 2 is administered at least 2 h after the start of Dose 1
	Dose 2: Oral administration of 2 sachets (101.91 g) PLENVU Dose 2 (containing sodium ascorbate, PEG 3350, ascorbic acid and electrolytes), to be reconstituted with water and made up to 473 mL and 473 mL of additional water to be consumed; both to be consumed over a period of 60 min after the start of Dose 2. Additional water may be drunk *ad libitum* during and after the dose.

Pharmacokinetic Assessments:

Blood samples will be taken pre-dose and up to 60 h after the start of Dose 1 (baseline samples at 1 and 2 h after the end of the evening meal on Day -1 and at 1 h before Dose 1, and post-dose samples at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h for the first 10 h then at 12, 16, 20, 24, 30, 36, 48 and 60 h) for the analysis of PEG 3350, ascorbate and potential related substances/metabolites (glycolic acid, oxalic acid, ethylene glycol and diethylene glycol). The following PK parameter estimates will be calculated for each analyte, where possible and appropriate.

- Cmax, Tlag, Tmax, AUC(0-last), AUC(0-inf), AUC(0-24), AUC%extrap, Lambda-z, T1/2

For analytes with endogenous levels, baseline adjustments will be performed prior to PK parameter estimations.
Pharmacodynamic Assessments: Pharmacodynamic parameters will include timing and number of bowel movements and time to achieve clear effluent.
Safety Assessments: Adverse events, clinical laboratory assessments, vital signs, electrocardiograms and physical examinations.
Statistical Methodology: No formal statistical analysis will be performed for the safety, PD or PK data; descriptive summaries are considered sufficient for this type of study.
Sample Size and Power: The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 18 subjects (maximum 20 subjects if replacement subjects are required) are to be enrolled to achieve a minimum of 12 evaluable subjects which are considered sufficient. A subject is considered evaluable if they have received 100% of each dose of PLENVU (i.e. Dose 1 and Dose 2), and 100% of the mandatory 473 mL additional water after each dose, have not vomited post-dose, and have sufficient PK, PD and safety data to meet the objectives of the study.

4 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus Disease 2019
CV%	Coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GC-MS	Gas chromatography-mass spectrometry
GCP	Good clinical practice
GP	General practitioner
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HPLC-MS	High performance liquid chromatography-mass spectrometry
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NSAID	Non-steroidal anti-inflammatory drugs
PD	Pharmacodynamics
PEG	Polyethylene glycol
PI	Principal investigator
PK	Pharmacokinetic(s)
QA	Quality assurance
QTc	corrected QT
RAP	Reporting and Analysis Plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure

SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event

5 Background Information

5.1 Introduction

In order to perform colonoscopy or colonic surgery effectively, it is necessary to empty the contents of the colon and cleanse the bowel. Effective cleansing of the colon requires the induction of copious watery diarrhoea. In the last 20 years, the use of electrolyte-balanced high molecular weight polyethylene glycol (PEG) 3350 (also known by its International Nonproprietary Name, “macrogol”, hereafter referred to as PEG)-based bowel lavage solutions has become the standard. It is commonly still required that patients ingest up to 4 L of solution (e.g. KLEAN-PREP®, GoLytely®) or 2 L of solution (MOVIPREP®) plus 1 L of additional clear fluid, usually in a split-dosing administration. Such volumes of bowel preparation fluid may interfere with compliance and hence the cleansing results and lesion detection achieved.

Studies have shown that formulating the osmotically active agents sodium ascorbate/ascorbic acid (also known as vitamin C) and sodium sulfate in combination with PEG 3350 enable a reduction in the volume of the PEG-based lavage solution.

PLENVU® (NER1006) [1] is a novel, low volume (1 L) PEG 3350 and ascorbate based bowel preparation that has been developed to provide whole bowel cleansing. It has a dual formulation containing an initial majority PEG dose followed by a majority ascorbate dose to maximise the overall effectiveness. This novel formulation addresses the challenges faced by patients to comply with drinking higher volume, 2 and 3 L, preparations. It may also contribute to the effectiveness of colonoscopy procedures at detecting colon cancer and for optimised bowel surveillance, through improved compliance with lower volume whilst maintaining effective bowel cleansing.

PLENVU has regulatory approval in 29 countries including the United States and 24 EU countries, Switzerland, Australia, New Zealand and South Korea, and has an agreed paediatric investigation plan. PLENVU was approved in the UK on 23 Oct 2017 (PL 20011/0040). The US Food and Drugs Administration (FDA) has a post approval requirement for an adult pharmacokinetic (PK) study including potential PEG metabolites, and the European Medicines Agency’s (EMA) Paediatric Committee and the FDA have requested that a programme of PK assessments be conducted in the paediatric population. The purpose of this adult study is to describe the systemic PK profile of PEG, ascorbate and any potential PEG metabolites of interest. The PK profiles identified in this adult study will be used to determine the blood sampling time points in the paediatric studies.

5.2 Investigational Medicinal Product

The following investigational medicinal product (IMP) will be used in this clinical study (Table 1).

Table 1 Investigational Medicinal Product

Investigational Medicinal Product	Dose and Route of Administration
PLENVU Powder for Oral Solution	Dose 1: Oral administration of 1 sachet (115.96 g) PLENVU Dose 1 (containing PEG 3350, sodium sulfate and electrolytes), to be reconstituted with water and made up to 473 mL and 473 mL of additional water to be consumed; both to be consumed over a period of 60 min after the start of Dose 1. Additional water may be drunk *ad libitum* during and after the dose.
	Rest period: Dose 2 is administered at least 2 h after the start of Dose 1
	Dose 2: Oral administration of 2 sachets (101.91 g) PLENVU Dose 2 (containing sodium ascorbate, PEG 3350, ascorbic acid and electrolytes), to be reconstituted with water and made up to 473 mL and 473 mL of additional water to be consumed; both to be consumed over a period of 60 min after the start of Dose 2. Additional water may be drunk *ad libitum* during and after the dose.

All IMP will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

5.3 Previous Study Findings

5.3.1 Nonclinical Findings

No non-clinical studies have been performed specifically with NER1006, now marketed as PLENVU. The non-clinical PK, pharmacodynamics (PD) and safety of the main constituents of PLENVU (PEG 3350, sodium sulfate, sodium ascorbate and ascorbic acid) are based on literature and available non-clinical studies conducted by Norgine with other PEG 3350 containing products, namely MOVICOL® and MOVIPREP®.

Based on the available literature, the hypothesis is that there will be minimal absorption of PEG 3350 following oral administration and that any absorbed material is likely to be excreted unchanged [2],[3],[4]. In addition, the absorption of ascorbic acid/sodium ascorbate and sodium sulfate is via a saturable process that in combination with their efficient renal clearance will maintain systemic exposure at a saturable threshold level. However, no formal studies have been performed to ascertain the actual PK profiles of potential PEG metabolites using validated Good Laboratory Practice (GLP) methods.

Preclinical studies of safety pharmacology, repeated dose toxicity, carcinogenicity, reproductive toxicity and genotoxicity provide evidence that PEG 3350, ascorbic acid and sodium sulfate have no significant toxic potential in humans.

5.3.2 Clinical Experience

The clinical development programme for PLENVU consists of one Phase I study (NER1006-01/2011 [OUT]), one Phase II study (NER1006-01/2012 [OPT]) and three Phase III studies (NER1006-01/2014 [NOCT], NER1006-02/2014 [MORA] and NER1006-03/2014 [DAYB]).

The OUT study was an open-label, randomised, sequential two-part (A and B), single centre Phase I study to investigate the PD evaluation of stool output following oral administration of various low volume PEG 3350-based gut cleansing solutions using a split-dosing regimen in healthy subjects. This study demonstrated that prototype PLENVU formulations met the study goal in relation to stool output as a surrogate marker

of efficacy. A high number of mostly mild to moderate gastrointestinal adverse events (AEs) were observed, possibly due in part to intolerance to the non-taste-optimised formulations as well as the young age of the healthy population (aged 18-45). The Phase I study established the principle that all the ascorbate components can be placed into one of the two doses and also established the optimal concentrations for the active ingredients.

The OPT study was an open-label, randomised, sequential two-part (A and B) Phase II study designed to conduct PK/PD and clinical evaluation of dose, taste- and flavour-optimised low volume PEG-based bowel cleansing solutions. The study was conducted in two parts. Part A was conducted in healthy subjects to evaluate the PD (principally stool output) and safety of the regimens to select the best-performing regimen for Part B. Part B was conducted in subjects undergoing a screening colonoscopy in order to evaluate bowel cleansing efficacy as determined by a colonoscopist and PK evaluations.

No major differences in PK activity of the different formulations was observed. Absorption of individual osmotically active components of formulations (especially the ascorbate) was small, in amounts that would not cause any clinical concern. From a PK perspective, all formulations tested were suitable for clinical use, but efficaciously, only two formulations were considered viable. One formulation was deemed suitable for further clinical studies when the additional required fluid intake volume was considered.

A Phase III programme of three studies investigating PLENVU was conducted following review of the efficacy and safety information gathered during the OUT and OPT studies. This Phase III programme included three non-inferiority studies, each versus one of three different bowel preparation comparators: trisulfate solution [SUPREP®]; MOVIPREP®; and sodium picosulfate + magnesium salt [CITRAFLEET®]. A total of 1985 randomised subjects were recruited across the three studies (of which 1134 to PLENVU). The studies were performed in the US and Europe, incorporating three different split-dosing regimens: first dose in the evening before colonoscopy, and second dose in the morning of the scheduled colonoscopy; or both doses taken the day prior to the colonoscopy; or both doses taken in the morning of the colonoscopy.

All studies had the same primary and secondary endpoints (alternative primary endpoints: overall bowel cleansing success rate and 'Excellent plus Good' cleansing rate in the colon ascendens as measured using the Harefield cleansing scale; key secondary endpoints: adenoma detection rate and polyp detection rate). The Phase III studies enrolled subjects undergoing screening, surveillance or diagnostic colonoscopy procedures.

In terms of safety, across the Phase III studies, the majority of treatment-emergent AEs (TEAEs) were mild or moderate in severity. The most common TEAEs were reported in the system order class of Gastrointestinal Disorders, as expected with a bowel cleansing agent. The most frequently reported TEAEs were nausea, vomiting, dehydration, abdominal pain/discomfort, glomerular filtration rate decreased, headache, fatigue, and gastritis. Nausea and vomiting were the most frequently reported IMP-related TEAEs. A total of five patients experienced serious TEAEs in the Phase III studies, all of which were considered unrelated to IMP. All serious TEAEs were mild to moderate in severity except for one event which was reported as severe. No deaths were reported in any of the Phase III studies. The majority of patients with available data had normal baseline results for haematology and clinical chemistry parameters that remained normal at each time point.

In terms of efficacy, all three Phase III studies showed non-inferiority versus their respective comparators for the alternative primary endpoints of overall bowel cleansing and 'excellent or good' cleansing of the colon ascendens. In both the NOCT and MORA studies, the overall bowel cleansing rates for PLENVU ranged from 85.1% (NOCT) to 92.0% (MORA 2-day-split dosing treatment arm). The 1-day morning split dosing regimen in MORA had an overall bowel cleansing rate of 89.1%. The overall cleansing rates were numerically greater for PLENVU than the comparator products. The results from the DAYB study show that the overall bowel cleansing rate in the PLENVU treatment group, although numerically greater than its comparator (62.0% versus 53.8%), was lower than that seen in the NOCT and MORA studies. A similar difference in cleansing rates was also apparent in the colon ascendens where an 'excellent plus good' rate of 4.4% for PLENVU (versus 1.2% for the comparator) was seen in the DAYB study versus rates of 31.6% to 35.9% in the NOCT and MORA studies for the PLENVU treatment groups. Both the 2-day and 1-day split dosing regimens of PLENVU were found to be superior to the comparator (MOVIPREP®) in the MORA study for 'excellent plus good' cleansing in the colon ascendens.

The following adverse reactions have been identified during post-approval use of another oral formulation of polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride or other polyethylene glycol (PEG)-based bowel preparations [1]:

- **Hypersensitivity:** urticaria/rash, pruritus, dermatitis, rhinorrhea dyspnea, chest and throat tightness, fever, angioedema, anaphylaxis and anaphylactic shock
- **Cardiovascular:** arrhythmia, atrial fibrillation, peripheral edema, asystole, and acute pulmonary edema after aspiration
- **Gastrointestinal:** upper gastrointestinal bleeding from a Mallory-Weiss tear, esophageal perforation [usually with gastroesophageal reflux disease (GERD)]
- **Nervous system***:* tremor, seizure

6 Rationale

6.1 Study Rationale

The purpose of this study is to determine if there is systemic exposure to components of the PLENVU formulation. If so, the plasma PK profiles for the components of PLENVU and their potential metabolites will be determined. In addition, this study aims to provide PK, PD, safety and tolerability results to support the design of paediatric studies for PLENVU.

The active ingredients of PLENVU, PEG 3350 and ascorbate, and potential metabolites, oxalic acid, glycolic acid, ethylene glycol and diethylene glycol will be analysed by a validated bioanalytical method and PK parameters will be derived from the concentration data where possible.

The ethylene glycol and diethylene glycol bioanalytical method using high performance liquid chromatography-mass spectrometry (HPLC-MS) could not be validated in line with EMA and FDA bioanalytical method validation guidelines as there was an unresolvable contamination present that interfered with the quantification of absolute values between samples processed and analysed in separate batches. The method is therefore deemed unsuitable to accurately quantify absolute ethylene glycol and diethylene glycol concentrations in human plasma for PK purposes. The method, however, did control the contamination sufficiently to demonstrate suitable accuracy and precision within batches of samples processed and analysed together. Therefore, it is considered that the method would be suitable to quantify changes in plasma concentrations from baseline for subject samples that are prepared and analysed within the same analytical batch. The sponsor concludes that the ethylene glycol and diethylene glycol method validation is fit for purpose to support its use as an exploratory tool to determine changes in ethylene glycol and diethylene glycol concentrations in plasma samples processed and run within the same batch. Full PK parameter estimations will not be calculated from concentration data generated from this analysis. A validated bioanalytical method for the analysis of ethylene glycol and diethylene glycol using a gas chromatography-mass spectrometry (GC-MS) method has been developed and will be used to characterise the PK profiles of ethylene glycol and diethylene glycol. As the validated bioanalytical method has low sensitivity, the exploratory objective to analyse ethylene glycol and diethylene glycol using the more sensitive HPLC-MS method will remain unchanged.

6.2 Dose Rationale

The dose selected for this study is the dose that has been approved by regulatory agencies in the US and Europe; i.e. it is the therapeutic dose and has been shown to be well-tolerated in previous studies. The regimen selected is based on the morning only regimen where the product is taken in the shortest timeframe, in line with the approved label, where any PK exposure to both active ingredients and their metabolites will be at their greatest.

6.3 Population Rationale

As this is a Phase I study to investigate the PK of a powder for oral solution formulation of PLENVU, the most relevant population is healthy subjects, which allows characterisation of safety, tolerability, PD and PK in a homogenous population without potential biases from a patient population. The FDA [5] and the EMA [6] recommends including participants aged 18 years and older with normal weight, who are non-smokers, without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non-compliance. As the study is to select the PK time points for a paediatric study, only young adults will be included in this study as these subjects will more closely reflect the paediatric population. Therefore, this study will enrol healthy male and female participants aged between 18 to 30 years.

6.4 Risks and Benefits

6.4.1 Risks Associated with the Administration of PLENVU

Diarrhoea is an expected outcome of bowel preparation. Due to the nature of the intervention, undesirable effects can occur in a significant number of patients during the process of bowel preparation. Whilst these vary between preparations, nausea, vomiting, bloating, abdominal pain, anal irritation commonly occur in patients undergoing bowel preparation. Dehydration may occur as a result of diarrhoea and/or vomiting.

From clinical studies in over a thousand subjects treated with PLENVU, the following TEAEs were considered common (i.e., frequency ≥1/100 to <1/10): vomiting, nausea and dehydration. The following treatment-emergent AEs were considered uncommon (i.e., frequency ≥1/1000 to <1/100): abdominal distension, anorectal discomfort, abdominal pain, upper abdominal pain, lower abdominal pain, drug hypersensitivity, headache, migraine, somnolence, thirst, fatigue, asthenia, chills, pains, aches, palpitations, sinus tachycardia, transient increase in blood pressure, hot flush, transient increase in liver enzymes, hypernatraemia, hypercalcaemia, hypophosphataemia, hypokalaemia, decreased bicarbonate, anion gap increased/decreased, hyperosmolar state. No AEs with a frequency of very common (i.e., frequency ≥1/10) were reported during clinical trials.

Allergic reactions including urticaria, oedema, rash and anaphylaxis have been reported rarely following exposure to PEG 3350.

Previous preclinical studies have provided evidence that the main active ingredients in PLENVU have no significant systemic toxicity potential.

Subjects will be monitored throughout the study for occurrence of AEs. Due to the nature of the expected outcome subjects will be dosed in small groups with convenient access to toilets.

6.4.2 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the study which will be conducted during the Coronairus Disease 2019 (COVID-19) pandemic.

6.4.2.1 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a subject developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP has been considered alongside available preclinical and clinical data (including class effects) and it is considered that a subject would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy subjects enrolled in the study.

6.4.2.2 General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient Sciences' monitoring and prevention control measures.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

6.4.3 General Risks and Overall Risk-Benefit Assessment

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

There is no benefit to the subjects from taking part in this study. However, the results obtained in this study will be of benefit in developing this bowel cleansing product to be used in a paediatric population.

The overall risk benefit balance is therefore considered to be acceptable.

7 Objectives and Endpoints

7.1 Objectives

7.1.1 Primary Objective

The primary objective is to characterise the PK profile of active ingredients of PLENVU, PEG 3350, ascorbate and potential related substances/potential metabolites (oxalic acid and glycolic acid using HPLC-MS, and ethylene glycol and diethylene glycol using GC-MS).

7.1.2 Secondary Objectives

The secondary objectives include the safety, tolerability and PD characterisation of PLENVU (1-Day Morning Only-Dosing) in healthy adult subjects.

7.1.3 Exploratory Objective

The exploratory objective of the study is to measure plasma concentrations of ethylene glycol and diethylene glycol using HPLC-MS.

7.2 Endpoints

Primary: PK parameters of the key active ingredients of each formulation of PLENVU, i.e. PEG 3350, ascorbate and potential related substances/metabolites (oxalic acid and glycolic acid [HPLC-MS], and ethylene glycol and diethylene glycol [GC-MS]).

Secondary: Safety parameters including: physical examination, clinical laboratory assessments, vital signs, electrocardiograms (ECGs) and AEs; and PD parameters including: timing and number of bowel movements and time to achieve clear effluent.

Exploratory: To evaluate plasma concentrations of ethylene glycol and diethylene glycol following dosing with PLENVU compared to pre-dose samples (HPLC-MS).

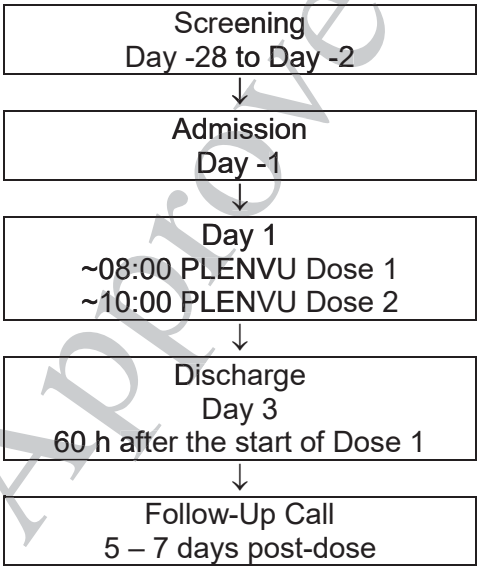
8 Study Design

8.1 Study Plan

This is a single centre, open-label, non-randomised, study in healthy adult subjects to investigate the PK of PLENVU as a powder for oral solution formulation (PLENVU Dose 1 and PLENVU Dose 2). It is planned to enrol up to 18 healthy adult male and non-pregnant, non-lactating female subjects to ensure 12 evaluable subjects complete the study. A subject is considered evaluable if they have received 100% of each dose of PLENVU (i.e. Dose 1 and Dose 2), and 100% of the mandatory 473 mL additional water after each dose, have not vomited post-dose, and have sufficient PK, PD and safety data to meet the objectives of the study. Subjects will receive PLENVU on Day 1, with at least a 2 h period between the start of each dose. All subjects will receive the powder for oral solution formulations in the same order, i.e. PLENVU Dose 1, containing PEG 3350, sodium sulfate and electrolytes, followed by PLENVU Dose 2, containing sodium ascorbate, PEG 3350, ascorbic acid and electrolytes. Details of the IMP are provided in Section 5.2.

The study design is presented in Figure 1. Subjects will be screened for inclusion in the study up to 28 days before dosing. Eligible subjects will be admitted in the afternoon (approximately 16:00) on the day before dosing (Day -1). Subjects will receive a standardised evening meal. At approximately 08:00 on Day 1, subjects will receive PLENVU Dose 1, reconstituted with water and made up to 16 US fl oz (473 mL), and 473 mL of additional water, both to be consumed over a period of 60 min after the start of Dose 1. Dose 2 will be administered at least 2 h after the start of Dose 1. At approximately 10:00, PLENVU Dose 2, reconstituted with water and made up to 16 US fl oz (473 mL), and 473 mL of additional water will be administered in the same manner as PLENVU Dose 1, and both to be consumed over a period of 60 min after the start of Dose 2. Additional water may be drunk *ad libitum* during and after each dose. Blood samples will be taken at 1 and 2 h after the end of the evening meal on Day -1, 1 h before Dose 1 and serially from Dose 1 until 60 h after the start of dosing of PLENVU Dose 1, and safety assessments will be performed throughout the study. Subjects will be discharged from the clinic at 60 h after the start of dosing for PLENVU Dose 1, following completion of the PK and safety assessments. There will be a follow-up call 5 to 7 days after dosing to ensure the ongoing wellbeing of subjects.

Figure 1 Study Sequence



8.2 Criteria for In-Study Decisions

Not applicable.

8.3 Subject Withdrawal

If a subject wishes to leave the study at any time, they will be permitted to do so. Every reasonable effort will be made by Quotient Sciences to complete final assessment/discharge procedures. Quotient Sciences will advise the sponsor of the withdrawal of any subject from the study drug(s).

Subjects will be withdrawn from the study drug(s) for the following reasons:

- Experiencing a serious or severe AE including but not limited to:
  - corrected QT (QTc) interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)
  - alanine aminotransferase (ALT) concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Pregnancy
- Termination of the study
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness or requirement for prohibited medication
- Any current evidence of SARS-CoV-2 infection
- Unable to consume 100% of either PLENVU Dose 1 or Dose 2
- At the discretion of the investigator

For the purpose of withdrawal criteria, baseline will be considered as the pre-dose Day 1 measurement.

For a subject who withdraws because of an IMP-related AE, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the study prematurely because of an IMP-related AE or termination of the study will be considered to have completed the study, and will not be replaced.

Subjects withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor.

8.4 Subject Replacement

Up to 2 replacement subjects may be enrolled into the study. The maximum number of subjects that may be dosed is 20.

Subjects withdrawn due to an IMP-related AE (with the exception of IMP-related vomiting) or termination of the study will not be replaced.

Subjects who are withdrawn for other reasons may be replaced at the discretion of the investigator and sponsor to ensure sufficient evaluable subjects.

A subject is considered evaluable if they have received 100% of each dose of PLENVU (i.e. Dose 1 and Dose 2), and 100% of the mandatory 473 mL additional water after each dose, have not vomited post-dose, and have sufficient PK, PD and safety data to meet the objectives of the study.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated, prior to a decision as to whether to terminate the study if any of the following criteria are met:

- A serious adverse reaction (i.e. a SAE considered at least possibly related to the IMP administration) in one subject.

- Severe non-serious adverse reactions (i.e. severe non-serious AE considered as, at least possibly related to the IMP administration) in two subjects, independent of within or not within the same system organ class.

Relatedness will be determined by the investigator. If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

8.6 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The early termination of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow-up measures taken for safety reasons if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the principal investigator (PI) or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require temporary suspension or early termination of the study.

- The occurrence of serious or severe AE(s), as defined in Section 8.5, if considered to be related to the IMP, as defined in Section 14.2.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

If any of the above occurs, the study may be terminated if careful review of the overall risk/benefit analysis described in Section 6.4 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

8.7 Treatment Allocation

This is an open-label, non-randomised study, therefore a randomisation schedule will not be produced. A treatment allocation list will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The treatment allocation list will be retained in the Investigator Site File.

8.7.1 Subject Numbers

Subject numbers will be allocated on the morning of dosing according to the code 001 to 018 using the lowest number available. Replacement subjects will be allocated subject numbers 901 to 918, where the last 2 digits are the same as those of the original subject (e.g. if Subject 005 withdraws, the replacement will have Subject Number 905).

8.7.2 Blinding

This is an open-label, non-randomised study and therefore blinding is not required.

9 Selection of Subjects

Quotient Sciences must have a full medical history from each subject's general practitioner (GP) within the last 12 months, prior to enrolment in the study.

Subjects will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before subjects are admitted to the clinic, The Over Volunteering Prevention System will be checked to ensure that each subject has not participated in a study at any site within at least 3 months of the dosing date.

9.1 Informed Consent

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an informed consent form (ICF).

9.2 Inclusion Criteria

1. Healthy males or non-pregnant, non-lactating healthy females.
2. Age 18 to 30 years
3. Body mass index of 18.0 to 35.0 kg/m^2
4. Must be willing and able to communicate and participate in the whole study
5. Must provide written informed consent
6. Must agree to use an adequate method of contraception (as defined in Section 9.4)

Inclusion criteria 4 and 6 from the list above will be re-assessed at admission/pre-dose.

9.3 Exclusion Criteria

1. Subjects who have received any IMP in a clinical research study within the previous 3 months
2. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
3. Subjects who have previously been enrolled in this study.
4. History of any drug or alcohol abuse in the past 2 years
5. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine)

6. Current smokers and those who have smoked within the last 12 months. A breath carbon monoxide reading of greater than 10 ppm at screening and at admission
7. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
8. Females who are pregnant or lactating (all female subjects must have a negative urine pregnancy test at screening and admission).
9. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening
10. Clinically significant abnormal biochemistry, haematology or urinalysis as judged by the investigator at screening (laboratory parameters are listed in Appendix 1)
11. Evidence of dehydration or abnormal electrolyte levels. Clinical evidence or suspicion of significant dehydration at admission/pre-dose.
12. History or evidence of any clinically relevant ECG abnormality and hypertension
13. Positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)
14. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results
15. History of clinically significant cardiovascular, renal, hepatic, chronic respiratory or psychiatric disorder, as judged by the investigator
16. History or presence of organic or functional gastrointestinal conditions (e.g. chronic constipation, inflammatory bowel disease or irritable bowel syndrome)
17. Previous or current relevant abnormal gastrointestinal motility according to clinical judgement
18. History or presence of any clinically significant acute illness within 28 days prior to the first dose of IMP based on clinical judgement at screening or admission
19. History of any of the contraindications mentioned in the PLENVU Summary of Product Characteristics (SmPC) [7]
20. Clinically relevant findings on physical examination based on investigator judgement
21. Donation or loss of greater than 500 mL of blood within the previous 8 weeks
22. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (other than hormonal contraception and occasional use of non-steroidal anti-inflammatory drugs [NSAIDs] and paracetamol) or herbal remedies in the 28 days before IMP administration (see Section 11.4). Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as agreed by the PI and sponsor's medical monitor.
23. Use of laxatives and gastrointestinal motility altering drug in the last 3 months
24. Evidence of current SARS-CoV-2 infection
25. Subjects who are ordered to live in an institution on court or authority order
26. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 5, 6, 8, 11, 12, 13, 18, 22, 23, 24 and 26 from the list above will be re-assessed at admission/pre-dose.

Healthy subjects who do not meet the inclusion/exclusion criteria for a study should not be enrolled into the study without exception.

9.4 Contraception

Male subjects who are sexually active with a partner of child bearing potential must use, with their partner, a barrier method of contraception (e.g. condom) from the time of informed consent until the last follow-up call.

Female subjects who are sexually active and of childbearing potential must use, with their partner, an approved method of effective contraception from the time of informed consent until at least 30 days post-dose.

The following methods are acceptable:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

- Progestogen-only hormonal contraception:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system

- Implantable intrauterine device

- Vasectomised partner

- Bilateral tubal ligation

- Male condom* with either female cap or diaphragm with spermicidal foam/gel/film/cream/suppository (double barrier)

* A female condom and a male condom should not be used together as friction between the two can result in either product failing.

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

Female subjects who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential unless post-menopausal or permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

9.4.1 Exposure to Partners During the Study

There may be a risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male subjects. Therefore, a condom should be used by all male subjects throughout the study until the last follow-up call.

9.4.2 Sperm Donation

Male subjects should not donate sperm for the duration of the study and until the last follow-up call.

9.5 Pregnancy

Subjects will be instructed that if they/their partner become pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject/subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery. Any subject reporting a pregnancy during the study will be discontinued from the study treatment and every reasonable effort will be made by Quotient Sciences to follow up the pregnancy until delivery.

A pregnancy notification form and follow-up will be completed.

9.6 Additional Study Restrictions

The following additional restrictions will be in place for the duration of the study:

1. Subjects must abstain from alcohol during the 24 h prior to screening and the 24 h prior to admission until 60 h after the start of Dose 1
2. Subjects must not drink liquids or eat food containing grapefruit, cranberry, caffeine or other xanthines (including tea and coffee) from 24 h prior to admission until 60 h after the start of Dose 1
3. Subjects must not take vitamin C or multivitamin supplements or drink liquids or eat food containing vitamin C such as citrus fruits from 24 h prior to admission until 60 h after the start of Dose 1
4. Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to admission until 60 h after the start of Dose 1
5. Subjects must consume a bowel preparation diet on Day -1 (light breakfast, light lunch and clear soup and/or plain yoghurt by 20:00)
6. Subjects must not take part in any unaccustomed strenuous exercise during the 72 h before the screening visit and then from 72 h prior to admission until discharge from the study.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments in Appendix 2, and in accordance with Quotient Sciences standard operating procedures (SOPs) unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose, all subjects will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the study flow chart in Appendix 2.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the investigator.

Subjects previously screened generically may participate in this study provided they meet the subject selection criteria. Procedures required by this protocol will only be done if they were not performed during generic screening. All screening data must be obtained within 28 days prior to administration of study medication, as stipulated above.

10.1.1 Subject Re-Screening

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e. has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

10.2 Admission and Pre-dose Procedures

The identity of the subjects will be confirmed at admission and pre-dose.

In addition, the ongoing eligibility of subjects will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

Reserve subjects for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days.

The subjects will be admitted to the clinical unit in the afternoon of the day before dosing (Day -1).

The admission and pre-dose procedures are presented in Appendix 2.

10.3 Study Day Procedures

10.3.1 Blood Volume

The total blood volume for each subject will not exceed 550 mL in a 4 week period.

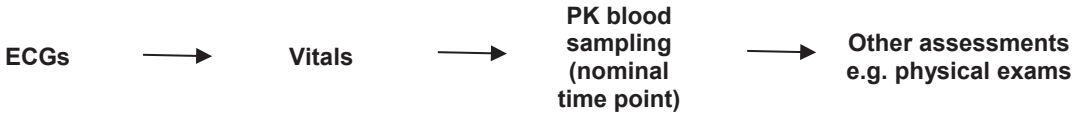
The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances the following will apply to post-dose time points:

- Pharmacokinetic samples should take priority over other procedures scheduled at the same time point and will be taken at the nominal time point.
- Electrocardiograms and vital signs should be taken before the PK sample when scheduled at the same time point
- Electrocardiograms should be taken before vital signs when both measurements are scheduled at the same time point
- Other assessments, eg physical examinations, will be performed within the required time windows

As guidance, the preferred order of assessments is:



All safety and PK assessments will be timed and performed relative to the start of the first dose (i.e. Dose 1).

The acceptable deviations from the nominal time points are presented in Appendix 3.

10.3.3 Discharge from the Clinical Unit

A subject will be allowed to leave the premises following completion of study-specific procedures at 60 h after the start of PLENVU Dose 1, providing that:

- no AEs have been reported during the study visit
- the subject responds in the affirmative when asked if they are feeling well

If any of these conditions are not met, then the subject will only be allowed to leave the clinical unit with the authorisation of the investigator or appropriately qualified delegate.

10.3.4 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines, each subject will receive a card stating the telephone number of the investigator.

10.3.5 Follow-up

A follow-up phone call will take place approximately 5 to 7 days after dosing to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs which can present a cause for concern, they will be required to attend the clinic for a further follow-up assessment (as an unscheduled visit). Completion of the last follow-up call or unscheduled follow-up visit will be considered the end of the study.

11 Dosing of Subjects

11.1 Food and Fluid Intake

Meals will be provided. On Day -1, subjects will be required to consume a bowel preparation diet. This will comprise a light breakfast and a light lunch. In the evening of Day -1, subjects will consume clear soup and/or plain yoghurt for the evening meal. This must be completed by 20:00. Subjects will then fast from all food and drink (except water) for a minimum of 12 h prior to dosing, and until approximately 5 h after the start of PLENVU Dose 2, at which time a standard lunch will be provided. An evening meal will be provided at approximately 11 h after the start of PLENVU Dose 1 and an evening snack at approximately 14 h after the start of PLENVU Dose 1. On subsequent days, meals will be provided at appropriate times.

Subjects will be allowed water *ad libitum* throughout the study.

The amount and time of fluid consumed from the start of Dose 1 until discharge from the clinic will be recorded for each subject. Any doses that take longer than 60 min will be recorded as a protocol deviation.

11.2 Administration of Test Preparations

Specific details of IMP(s), and doses to be administered are provided in Section 5.2 and Section 8.1, respectively.

The exact time of dosing will be decided based on logistics. The start and stop time of each dose of PLENVU and each 473 mL additional fluid will be recorded for each subject.

Subjects will receive the powder for oral solution formulation of PLENVU on the morning of Day 1. The formulation consists of Dose 1 and Dose 2. PLENVU Dose 1 will be reconstituted in water and made up to 473 mL (16 US fl oz). This will be administered at approximately 08:00, and consumed with an additional 473 mL water (the consumption of this 473 mL water is mandatory) over a period of 60 min after the start of Dose 1. Dose 2 will be administered at least 2 h after the start of Dose 1. Subjects will receive PLENVU Dose 2 at approximately 10:00, in the same manner as PLENVU Dose 1. PLENVU Dose 2, reconstituted in water and made up to 473 mL (16 US fl oz), and the additional 473 mL of water (the consumption of this 473 mL water is mandatory) will be consumed over a period of 60 min after the start of Dose 2. Additional water may be drunk *ad libitum* during and after each dose.

All fluid consumed from the start of Dose 1 until discharge from the clinic will be recorded for each subject.

11.3 Dosing Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration.

For each PLENVU dose and additional 473 mL water, the date and start and stop times, along with the amount of each dose consumed and the amount of additional water consumed will be recorded for each subject. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject can continue in the study.

11.4 Prior and Concomitant Medications

No medication will be permitted from 28 days before IMP administration until the follow-up call except hormonal contraception and occasional use of NSAIDs and paracetamol, and those deemed necessary by the investigator to treat AEs (see also Section 9.3). Any medications used will be recorded for each subject.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

12 Assessment of Efficacy

Not applicable for this Phase I study.

13 Assessment of Pharmacokinetics and Pharmacodynamics

13.1 Assessment of Pharmacokinetics

Venous blood samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study. Samples will be processed to isolate plasma and PK analysis will be carried out on plasma samples.

Plasma samples are sent for laboratory testing in linked anonymised form (subject number only). This information is able to be linked directly to the volunteer by the Quotient Sciences research team and study monitor, however not by the laboratory staff or sponsor.

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture according to the time schedule presented in Appendix 2.

Baseline samples will be collected at 1 and 2 h after the end of the evening meal on Day -1 and at 1 h before Dose 1. Post-dose samples will be collected at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h for the first 10 h, then at 12, 16, 20, 24, 30, 36, 48 and 60 h after Dose 1.

The acceptable deviation from the baseline sampling times is: within ± 10 min of the nominal sampling time.

The acceptable deviations from the nominal post-dose (post-dose is defined as any assessment performed after the start of Dose 1) blood sampling times are as follows:

- 1 to 16 h post-dose samples will be taken within ± 10 min of the nominal post-dose sampling time
- >16 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time if subjects are resident in the clinic

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the Clinical Sample Processing Manual.

Samples will be shipped to Unilabs - York Bioanalytical Solutions Ltd for the analysis of glycolic acid and the exploratory analysis of ethylene glycol and diethylene glycol, to Charles River Laboratories for the primary analysis of ethylene glycol and diethylene glycol and to Covance for the analysis of PEG 3350, ascorbate and oxalic acid.

PK parameters will be determined for PEG 3350, ascorbate, oxalic acid, glycolic acid, ethylene glycol and diethylene glycol as described in Section 15.3.

13.2 Assessment of Pharmacodynamics

The following PD parameters will be assessed in this study: the timing and the number of bowel movements and the time to achieve clear effluent (Appendix 2). The time of each bowel movement will be recorded for each subject, and the number of bowel movements after each dose per subject will be derived. Additionally, each bowel movement will be visually inspected in the toilet bowl by clinical staff and scored and recorded in the source data using the following 4-point scale (adapted from the stool characteristics rating tool [8]):

A. Clear contents (may be coloured but able to visualise the bottom of the toilet bowl)
B. Turbid contents
C. Opaque contents (dark and murky)
D. Any solid/semi-solid faecal material (irrespective of size) in the toilet bowl

Each bowel movement passed by subjects while resident in the clinic (up to 60 h after the start of Dose 1) will be inspected and assessed against the Bristol Stool chart.

Time to achieve clear effluent will be derived using the first bowel movement that can be described as clear effluent as recorded in the source data. The data may be used to determine the duration of the PD effects.

14 Assessment of Safety

14.1 Definition and Classification of Adverse Events

An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An adverse drug reaction is any AE where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related).

Adverse events will be monitored from the time the subject signs the ICF until after the final follow-up call. The severity of AEs should be assessed as follows:

Mild An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities

Moderate An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed

Severe An AE that prevents normal everyday activities; treatment or other intervention usually needed

14.2 Assessment of Causality

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the IMP. The temporal relationship of the event to IMP administration should be considered in the causality assessment (i.e. if the event starts soon after IMP administration and resolves when the IMP is stopped).

Causality should be assessed using the following categories:

Unrelated: Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP

Possibly related: Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals

Related: Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, e.g. natural history of the underlying disease, concomitant therapy, etc) will be determined by how well the experience can be understood in terms of one or more of the following:

- known pharmacology of the IMP
- reactions of a similar nature have been previously observed with the IMP or this class of drug

- the experience being related by time to IMP administration, terminating with IMP withdrawal or recurring on re-challenge
- alternative cause

14.3 Recording Adverse Events

AEs will be recorded from the time of providing written informed consent until discharge from the study at the follow-up visit/call. During each study visit the subject will be questioned directly regarding the occurrence of any adverse medical event according to the schedule in the clinical database. All AEs, whether ascribed to study procedures or not, will be documented immediately in the source data and reported in the case report form. This will include the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the investigator.

Any subject who withdraws from the study due to an AE will be followed up until the outcome is determined and written reports provided by the investigator.

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- an important medical event as recognised by the PI

SAEs must be reported to the sponsor immediately and within 24 h of becoming aware of the occurrence of an SAE. Full details on SAE reporting are included in the Safety Management Plan.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to an IMP and are both unexpected (i.e. the nature or severity is not expected from the information provided in the SmPC) and serious. SUSARs are subject to expedited reporting to the MHRA and EC (see Section 16.3.2 for details on reporting SUSARs).

14.5 Laboratory Measurements

Venous blood and urine samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study.

Blood and urine samples are sent for laboratory testing in linked pseudonymised form (subject number, initials [urine samples only], the subject's gender and date of birth for analytical reasons [blood samples only]). This information is able to be linked directly to the volunteer by the Quotient Sciences research team and study monitor, however, not by the laboratory staff or sponsor.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. The research will not involve analysis or use of human DNA.

Blood and urine samples results will be reviewed by a physician and acted upon before the subject is dosed or receives their next dose, or is released from the study, as is appropriate. A list of the laboratory parameters measured is presented in Appendix 1.

14.5.1 Haematology and Clinical Chemistry

Laboratory tests will be performed by The Doctors Laboratory according to the time schedule presented in Appendix 2. Blood samples will be collected and processed as detailed in the Clinical Sample Processing Manual.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- The pre-dose blood sample will be taken ≤1 h before dosing
- Post-dose blood samples will be taken ± 1 h from the nominal blood sampling time.

Creatinine clearance will be calculated by The Doctors Laboratory using the Cockcroft-Gault equation and body weight for eligibility purposes:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{(140-age [years]) x (body weight [kg]) (x C)}}{\text{serum creatinine (µmol/L)}}$$

Where correction factor C is 1.23 for men and 1.04 for women

14.5.2 Urinalysis

Urinalysis will be performed on-site using a dipstick according to the time schedule presented in Appendix 2. Urine samples will be collected and processed as detailed in the Clinical Sample Processing Manual. If microscopy is required, a urine sample will be sent to The Doctors Laboratory.

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time

14.5.3 Pregnancy Test

Urine pregnancy tests will be performed as detailed in Appendix 2. The samples will be collected and processed as detailed in the Clinical Sample Processing Manual.

14.5.4 Drug Screen

A urine drug screen will be performed on-site using a dipstick method according to the time schedule presented in Appendix 2. The sample will be collected and processed as detailed in the Clinical Sample Processing Manual. Subjects will be screened for the drugs of abuse listed in Appendix 1.

14.5.5 Alcohol Breath Test

An alcohol breath test will be performed according to the time schedule presented in Appendix 2. A positive result will exclude the subject from dosing during that admission.

14.5.6 Carbon Monoxide Breath Test

A carbon monoxide breath test will be performed according to the time schedule presented in Appendix 2. A result of greater than 10 ppm will exclude the subject from the study.

14.5.7 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken e.g. the subject will not be entered into the study or the subject may be withdrawn from the study. The subject will be referred to their GP or other appropriate healthcare provider for further care. The same will apply if the results of the HBsAg, HCV Ab or HIV test are positive and in addition the investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the investigator believes the results may be of clinical significance.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator.

14.6 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the subject has been in a supine position for a minimum of 5 min according to the time schedule presented in Appendix 2. Oral temperature will be measured at screening. The acceptable deviations from the nominal vital signs measurement time points are:

- The pre-dose vital signs measurements will be taken ≤2 h before dosing.
- Post-dose vital signs measurements will be taken ± 30 min from the nominal post-dose time points.
- Discharge vital signs measurements will be taken ± 1 h from the nominal time point.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

14.7 ECG Measurements

12-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min as detailed in Appendix 2. The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken ≤2 h before dosing
- Post-dose ECG measurements will be taken ± 30 min from the nominal post-dose time point.
- Discharge ECG measurements will be taken ± 1 h from the nominal time point.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.

Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

14.8 Body Weight and Height

The subject's body weight and height will be measured as detailed in Appendix 2.

14.9 Physical Examination

Subjects will undergo a physical examination as detailed in Appendix 2.

14.10 Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed, if it is believed that an important effect of the IMP(s) is occurring or may occur at a time when no measurements are scheduled, or if extra procedures are needed in the interests of safety.

Additional blood samples for safety assessments may be taken if required by the investigator at any point.

15 Statistics and Data Analysis

15.1 Sample Size Justification

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 18 subjects (maximum 20 subjects if replacement subjects are required) are to be enrolled to achieve a minimum of 12 evaluable subjects which are considered sufficient.

15.2 Data Management

Data management will be performed by Quotient Sciences.

Study data will be managed using a validated electronic case report form (eCRF) database system and subjected to data consistency and validation checks. Data queries will be raised within the study eCRF database by data management staff and resolved with the assistance of clinical staff.

AEs and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v23.0 or the most recent version available at the time coding commences) and the World Health Organisation (WHO) Drug Dictionary Global Drug Reference List (2020 or the most recent version available at the time coding commences), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and haematology data (and other safety laboratory data) will be collected by a central laboratory (The Doctors Laboratory) and stored electronically in their clinical pathology system. The data will be transferred electronically to Quotient Sciences and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the Data Management Plan are met.

Further details are addressed in the Data Management Plan.

15.3 Pharmacokinetic Data Analysis

The concentration data for PEG 3350, ascorbate and oxalic acid provided by Covance, ethylene glycol and diethylene glycol (GC-MS) provided by Charles River Laboratories and glycolic acid, provided by Unilabs - York Bioanalytical Solutions Ltd will be analysed by Quotient Sciences, using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA).

Concentration data will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters, where possible and appropriate:

- **Cmax:** maximum observed concentration
- **Tlag:** the elapsed time from first dose at which analyte was first quantifiable in a concentration vs time profile
- **Tmax:** the time from first dose at which Cmax was apparent
- **AUC(0-last):** area under the curve from 0 time to last measurable concentration
- **AUC(0-inf):** area under the curve from 0 time extrapolated to infinity
- **AUC(0-24):** area under the curve from 0 time to 24 h post-dose
- **AUC%extrap:** percentage of AUC(0–inf) extrapolated beyond last measured time point
- **Lambda-z:** the slope of the apparent elimination phase
- **T1/2:** the apparent elimination half-life

For analytes with endogenous levels, baseline adjustments will be performed prior to PK parameter estimations.

In addition, concentrations of ethylene glycol and diethylene glycol (HPLC-MS) provided by Unilabs - York Bioanalytical Solutions Ltd and change from baseline will be presented for the exploratory analysis.

Further details of the PK data analysis will be included in the Reporting and Analysis Plan (RAP).

15.4 Statistical Data Analysis

Production of summary tables, figures and listings for this study will be performed by Quotient Sciences using the statistical package SAS (v9.4 or more recent version).

No formal statistical analysis will be performed for this study. Descriptive statistics are considered adequate for a study of this type. In general terms categorical data (including treatment-emergent AEs) will be presented using counts and percentages, while continuous variables will be presented using mean, median, standard deviation, minimum, maximum. Additional statistics will be provided for PK-related data, including coefficient of variation (CV%), geometric mean, geometric CV% and geometric n (i.e. number of subjects with an observation that are included in the natural logarithmic transformation).

Descriptive summaries for all safety data (AEs, vital signs, ECGs and safety laboratory assessments) and PD data (timing and number of bowel movements, time to achieve clear effluent) will be provided (including changes from baseline as required).

Descriptive summaries for all PK data will also be provided, which will include baseline adjusted concentration data for endogenous compounds.

Populations for analysis will be determined for safety, PD and PK data after database lock when all the relevant data are available using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

Further details relating to the statistical analysis will be included in the study-specific RAP including the following:

- Criteria to be used to define each of the analysis populations
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn subjects

All safety, PD and PK data will be listed.

15.5 Interim Analysis

No formal interim analyses are planned for this study.

16 Safety Reporting to Ethics Committees and Regulatory Authorities

16.1 Events Requiring Expedited Reporting

SUSARs (Section 14.4.2) are subject to expedited reporting to the MHRA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important

- SAEs that occur after the subject has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects, such as:
    - an SAE which could be associated with the study procedures and which could modify the conduct of the study
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
    - any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same sponsor

16.2 Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed as soon as possible, irrespective of whether the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the ethics committee, as prior agreed with the sponsor.

16.3 Reporting

16.3.1 Reporting Serious Adverse Events

The investigator is required to notify the study sponsor within 24 h of becoming aware of the occurrence of an SAE or serious adverse reaction. A copy of the written report of the event should promptly be sent to the study sponsor for information purposes, in accordance with ICH guidelines for GCP.

16.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

16.3.3 Expedited Reporting of Events

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

The investigator, as and when prompted by the sponsor, is required to notify the EC of any fatal or life-threatening SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor to report other SUSARs to the MHRA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

The investigator, as and when prompted by the sponsor, is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

16.3.4 Reporting of Urgent Safety Issues

It is the responsibility of the sponsor to inform the appropriate competent authorities and the ethics committee within 3 calendar days of the urgent safety issue. This responsibility may be delegated to Quotient Sciences.

16.4 Serious Breaches

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

17 Protocol Amendments and Deviations

17.1 Amendments

After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

If the Participant Information Sheet and ICF are updated as a result of the substantial amendment, the new approved versions will be used to re-consent currently enrolled subjects and must be provided to additional subjects prior to their entry into the study.

17.2 Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source data as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8.3 have been met.

18 Regulatory

18.1 Compliance

This study will be conducted in accordance with the protocol and with the following legislation:

- International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 [9]
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [10]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [11]
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [12]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [13]

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [14].

18.2 Ethics Approval

Prior to the initiation of the study, the protocol and associated documentation must be given a favourable opinion by an EC. A copy of this written approval and any correspondence with the EC will be provided to the sponsor.

18.3 MHRA Approval

Prior to the initiation of the study, the Clinical Trial Authorisation application must be approved by the MHRA. A copy of this approval and any correspondence with the MHRA will be available at the clinical and sponsor sites. A copy of the MHRA approval will be provided to the EC.

18.4 Administration of Radiation

Not applicable.

18.5 Source Data

A study-specific source document identification list will be finalised with the sponsor prior to the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

For this study, electronic data capture will be used where possible and data will be automatically recorded into an eCRF. In instances where paper source documents are used, data to be transcribed into the eCRF will be identified using a Source Document Identification List, as governed by Quotient Sciences' SOPs.

18.6 Declaration of the End of the Study

The definition of the end of the study is defined as the last visit of the last subject (e.g. follow-up assessment or phone call). Any changes to this definition will be notified as a substantial amendment (see Section 17.1).

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

18.7 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters etc) will be kept in accordance with the ICH guidelines for Good Clinical Practice 1996, updated 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 (ICH GCP Section 4.9.5) [9], The Medicines for Human Use (Clinical Trials) Regulations 2004 [10] and The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [11],[12].

All study related documents will be retained for a minimum period of 5 years. After this time, the sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

18.8 Protection of Personal Data and Confidentiality

Personal data are securely stored to prevent unauthorised access, disclosure, dissemination, alteration or loss of information and unauthorised personal data processing. Access to personal information is restricted so that only personnel who are required to access personal data as part of their job role can do so. All personnel who access personal information are bound by a duty of confidentiality.

Technical arrangements surrounding the electronic storage and use of data are as follows:

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls
- Off-site personnel can only access networked computers through a virtual private network
- Electronic access of data is limited according to user roles
- All data are stored on password protected computers

Organisational arrangements are as follows:

- All buildings are secured by key-card access

- Manual files of personal data are stored within locked cabinets that can only be accessed by authorised personnel
- Data security and/or confidentiality provisions are utilised in agreements with third parties
- Documented Back-up and disaster recovery procedures are in place
- Internal audit and compliance functions provide regulatory oversight

The personal data of volunteers will be pseudonymised in that they will only include health, initials, date of birth and demographics (gender and ethnicity) and cannot be linked back to the individual by the recipient. The sponsor shall be the data controller in respect of the personal data of the study subjects collected in connection with the study, and shall act in accordance with the relevant data protection laws in relation to the collection and processing of those personal data. The study subjects' pseudonymised personal data shall be collected and processed for the purposes of the study and may also be added to research databases and used in the future by the sponsor and its affiliates for certain additional clinical research, for product regulation and safety reporting purposes and for ensuring compliance with legal requirements. The study subjects' pseudonymised personal data may be processed for such purposes by other parties including: the sponsor's affiliates and licensing partners, its business partners, regulatory agencies and other health authorities, and ECs. The study subjects' authorisation for such use and disclosure shall be obtained by the study subjects signing the ICF for the study.

Additionally, Quotient Sciences personnel are contractually bound by a duty of confidentiality and receive training on this matter.

18.9 Data Security Breach

Quotient Sciences has a comprehensive process in place for identifying, assessing, resolving and reporting any potential data security breach. All staff are trained in the identification of potential data security breaches. Potential breaches are managed by appropriately trained quality assurance personnel in accordance with Quotient Sciences' SOPs. After robust assessment of data breaches, those deemed serious will be reported to the sponsor and Information Commissioner's Office, as applicable.

19 Audit (Quality Assurance) and Inspection

This study may be subject to audit by the Sponsor or their representatives and Regulatory Authorities. These audits may be undertaken to check compliance with the requirements of GCP and can include:

- In-house study file audit
- Audit of Clinical Study Report
- Audit of selected study centres, requiring access to patient medical records, study documentation and facilities, laboratories or pharmacies used for the study.

The study centre, facilities and all data (including source data) and documentation will be made available for audit by the Investigator according to the ICH-GCP guidelines. The Investigator agrees to co-operate with the auditor during his/her visit and will be available to supply the auditor with e-CRF or other files necessary to conduct that audit. Any findings will be strictly confidential.

In the event that a Regulatory Authority informs the Investigator that it intends to conduct an inspection, the Sponsor must be notified immediately.'

19.1 Monitoring

GCP requires that studies are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. A study monitor, independent of Quotient Sciences, will be appointed to verify that the study is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The investigator agrees to receive visits from a study monitor and provide assistance to verify protocol implementation, source data completion and transcription of data into the electronic case report form, document storage and AE reporting.

Quotient Sciences will extend the professional privilege of access to the subjects' clinical source documents to the study monitor, EC, regulatory bodies or other authorised personnel (e.g. auditor) for the purposes of source data verification.

Following completion of the study both study related documents and subject data may be sent to the sponsor at a location outside of the UK where data protection laws differ. In the interests of confidentiality, subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained.

20 Finance and Insurance

The sponsor (Norgine Ltd) has funded this study. A no-fault clinical trials insurance has been obtained by the sponsor. The sponsor insurance will compensate subjects in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2012 edition [15].

21 Publication

Please refer to the Master Services Agreement for information on publication.

Quotient Sciences shall have no rights of publication concerning any connection with this study. Publication of study results in whole, or in part, shall be within the sole and absolute discretion of the sponsor. Results may not be presented, submitted for publication, published or referred to, in whole or in part by Quotient Sciences.

22 References

[1] Prescribing Information for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) [Package Insert] Norgine Limited [Revised May 2019] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209381

[2] Donovan MD, Flynn GL and Amidon GL. Absorption of polyethylene glycols 600 through 2000: The molecular weight dependence of gastrointestinal and nasal absorption. *Pharm Res*. 1990; 7 (8): 863-868.

[3] Koyama Y, Tateishi M, Kawaide A and Kojima S. Gastrointestinal absorption of [^{14}C]poly(ethylene glycol) 4000. *Polymer Journal*. 1992; 24 (6): 583-589.

[4] Brady CE 3rd, DiPalma JA, Morawski SG et al. Urinary excretion of polyethylene glycol 3350 and sulfate after gut lavage with a polyethylene glycol electrolyte lavage solution. *Gastroenterology*. 1986; 90 (6): 1914-1918.

[5] FDA Guidance: Food effect, bioavailability and fed bioequivalence studies. 2002.

[6] EMA – Guidance on the investigation of bioequivalence. 20 January 2010.

[7] Summary of Product Characteristics for PLENVU Powder for Oral Solution [Revised 27 Jan 2020] https://www.medicines.org.uk/emc/product/8578/smpc

[8] Hsu, W-F, Liang C-C, Lin C-K et al. A modified bowel preparation protocol improves the quality of bowel cleansing for colonoscopy. *Adv Dig Med*. 2016; 3 (3): 144-147.

[9] International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016.

[10] The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031.

[11] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928.

[12] The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984.

[13] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941.

[14] World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (and all subsequent amendments).

[15] Guidelines for Phase I Clinical Trials. Association of the British Pharmaceutical Industry Guidelines. London, UK; 2012 Edition (as amended 12/11/2014).

Appendix 1 Clinical Laboratory Parameters

Haematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Basophils	Alanine Aminotransferase (ALT)	Hepatitis B Surface Antigen	Bilirubin	Amphetamines
Eosinophils	Albumin	Hepatitis C Antibody	Blood	Barbiturates
Haematocrit	Alkaline Phosphatase	HIV Antibody	Glucose	Benzodiazepines
(Packed Cell Volume- PCV)	Anion Gap		hCG (all female subjects)	Cocaine
Haemoglobin	Aspartate Aminotransferase (AST)		Ketones	Marijuana/Cannabis
Lymphocytes	Bicarbonate		Leukocytes	Methadone
Mean Cell Haemoglobin (MCH)	Bilirubin (Total)		Nitrites	Methamphetamine/ Ecstasy
Mean Cell Haemoglobin Concentration (MCHC)	Bilirubin (Direct) (only if Total is elevated)		pH	Morphine/Opiates
Mean Cell Volume (MCV)	Blood Urea Nitrogen		Protein	Phencyclidine
Monocytes	Calcium		Specific gravity	Tricyclic Antidepressants
Neutrophils	Chloride		Urobilinogen	
Platelet Count	Creatine Kinase (CK)		**At discretion of investigator based on urinalysis results**	
Red Blood Cell (RBC) Count	Creatinine[a]		Microbiology	
White Blood Cell (WBC) Count	Gamma Glutamyl Transferase (GGT)		Urine Microscopy	
	Glucose			
	Glucose (Fasting)			
	Osmolality			
	Potassium			
	Phosphate (Inorganic)			
	Protein (Total)			
	Sodium			
	Uric acid			

[a] Creatinine clearance will be calculated from creatinine using the Cockcroft-Gault

Appendix 2 Study Flow Chart

Study Day	-28 to -2	-1			1													2				3		6-8
							Time After Start of Dose 1 (h)																		
	Screening	Admission	1 h post-evening meal	2 h post-evening meal	Pre-dose	0	1	2	3	4	5	6	7	8	9	10	12	16	20	24	30	36	48	60[e]	Follow-Up[g]
General Assessments																								
Informed Consent	X																							
Medical History	X	X[a]																						
Weight and Height	X																							
Vein Assessment	X																							
Carbon Monoxide Breath Test	X	X																						
Drug Screen	X	X																						
Alcohol Breath Test	X	X																						
Urine Pregnancy Test	X	X																						
IMP Administration						X		X																
Time and Amount of Fluid Consumed						←	→																	
Safety Assessments																								
Physical Examination	X																						X	
Safety Labs[b]	X				X												X						X	
Urinalysis	X	X															X						X	
ECG	X				X					X										X			X	
Vital Signs[c]	X				X					X										X			X	
Adverse Events	←																						→	
PD Assessments																								
Timing of Bowel Movements[i]						←																	→	
Time to Clear Effluent[h]						←																	→	
PK Assessments																								
Blood Samples for PK Analysis[d]			X	X	X		X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Update only
[b] Haematology and clinical chemistry at each time point including virology at screening
[c] Blood pressure and pulse rate. Oral temperature will be measured at screening only

[d] Time points are relative to the start of Dose 1. The following allowable time windows will apply: The baseline blood samples at 1 and 2 h after the end of the evening meal on Day -1 and 1 h pre-dose will be taken within ± 10 min of the nominal sampling time; 1 to 16 h post-dose samples will be taken within ± 10 min of the nominal post dose sampling time; >16 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time. At each time point, 5 blood sample tubes will be required (1 tube for PEG 3350 analysis, 1 tube for glycolic acid analysis, 1 tube for ascorbate and oxalic acid analysis, 1 tube for the primary analysis of ethylene glycol and diethylene glycol and 1 tube for the exploratory analysis of ethylene glycol and diethylene glycol)
[e] Subjects will be discharged from the clinic after the 60 h post Dose 1 assessments have been performed
[f] To be taken immediately before start of Dose 2
[g] A follow-up call will take place 5 to 7 days post-dose (i.e. Days 6 to 8)
[h] Refer to Section 13.2 for full details on assessing clear effluent
[i] Timing of bowel movements will be recorded from the start of Dose 1

Appendix 3 Time Point Windows

Item	Window	Reference Time Point
Blood Sampling (PK) (Baseline, Day -1)	± 10 min from nominal time	End of evening meal
Blood Sampling (PK) (Baseline 1 h pre-dose)	± 10 min from nominal time	Start of 1st oral dose of PLENVU
Blood Sampling (PK) (1 h to 16 h post-dose)	± 10 min from nominal time	Start of 1st oral dose of PLENVU
Blood Sampling (PK) (> 16 h post-dose)	± 30 min from nominal time	Start of 1st oral dose of PLENVU
Vitals signs (pre-dose)	≤ 2 h pre dose	Start of 1st oral dose of PLENVU
Vitals signs (post-dose)	± 30 min from nominal time	Start of 1st oral dose of PLENVU
Vital signs (Discharge)	± 1 h from nominal time	Start of 1st oral dose of PLENVU
ECGs (pre-dose)	≤ 2 h pre dose	Start of 1st oral dose of PLENVU
ECGs (post-dose)	± 30 min from nominal time	Start of 1st oral dose of PLENVU
ECGs (Discharge)	± 1 h from nominal time	Start of 1st oral dose of PLENVU
Urinalysis (post-dose)	± 2 h from nominal time	Start of 1st oral dose of PLENVU
Evening Snack (finish time)	≥ 12 h pre dose	Start of 1st oral dose of PLENVU