Synopsis

Sponsor: Norgine Ltd.	**Investigational Medicinal Product:** PLENVU® Powder for Oral Solution	**EudraCT No.:** 2017-003440-20 [redacted]
Title of Study: A Pharmacokinetic Study of PLENVU® in Healthy Subjects		
Principal Investigator: [redacted]		
Study Centre: [redacted]		

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.