Public Assessment Report

Decentralised Procedure

Plenvu powder for oral solution

(Macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride, potassium chloride)

Procedure No: UK/H/6370/001/DC

UK Licence No: PL 20142/0020

Norgine B.V.
LAY SUMMARY

Plenvu powder for oral solution

This is a summary of the Public Assessment Report (PAR) for Plenvu powder for oral solution (PL 20142/0020; UK/H/6370/001/DC). It explains how Plenvu powder for oral solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Plenvu powder for oral solution.

The product will be referred to Plenvu throughout the remainder of this public assessment report (PAR).

For practical information about using Plenvu, patients should read the package leaflet or contact their doctor or pharmacist.

What is Plenvu and what is it used for?
Plenvu contains the combination of active substances macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride.

Plenvu is a laxative.

Plenvu is intended for adults 18 years of age and older prior to any clinical procedure requiring a clean bowel.

How does Plenvu work?
Plenvu cleans the patient’s bowel by causing them to have diarrhoea.

How is Plenvu used?
The pharmaceutical form of Plenvu is a powder for oral solution and the route of administration is oral.
The patient’s treatment with Plenvu must be completed before their clinical procedure.

This course of treatment should be taken as divided doses as described below:

- **Two-day split dosing schedule**
  Dose 1 taken in the evening before the clinical procedure (approximately 18.00H) and Dose 2 in the early morning of the day of the clinical procedure (approximately 06.00H), or

- **Morning only dosing schedule**
  Dose 1 and Dose 2 taken in the morning of the day of the clinical procedure (Dose 1 at approximately 05.00H); the two doses separated by a minimum 1 hour interval, or

- **Day before dosing schedule**
  Dose 1 and Dose 2 taken in the evening of the day before the clinical procedure (Dose 1 at approximately 18.00H); the two doses separated by a minimum 1 hour interval.

The patient’s doctor will inform them which dosing schedule to follow. DO NOT add any other ingredients to the doses.

The patient can only consume food and drink in accordance with the details provided for the chosen schedule but must not eat while taking Plenvu and until after their clinical procedure.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.
The medicine can be obtained without a prescription.

**What benefits of Plenvu have been shown in studies?**

Plenvu is a fixed combination product of known active substances. The company provided its own data on efficacy and safety studies. These studies have shown that Plenvu is effective for bowel cleansing prior to any procedure requiring a clean bowel.

**What are the possible side effects of Plenvu?**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects with Plenvu (which may affect up to 1 in 10 people) are:
- Dehydration
- Nausea (feeling sick)
- Vomiting.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Plenvu, see section 4 of the package leaflet available on the MHRA website.

**Why is Plenvu approved?**

The MHRA decided that Plenvu’s benefits are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Plenvu?**

A risk management plan (RMP) has been developed to ensure that Plenvu is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Plenvu including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Plenvu.**

Austria, Belgium, Bulgaria, the Czech Republic, Germany, Denmark, Spain, Finland, France, Croatia, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, the Slovak Republic and the UK agreed to grant a Marketing Authorisation for Plenvu on 27 September 2017. A Marketing Authorisation was granted in the UK on 23 October 2017.

Austria, Netherldes and Spain agreed to grant a Marketing Authorisation with the name Pleinvue.

The full PAR for Plenvu follows this summary.

For more information about treatment with Plenvu read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Plenvu (PL 20142/0020; UK/H/6370/001/DC) could be approved. The product is available from a pharmacy without a prescription (legal classification P) and is indicated in adults for bowel cleansing prior to any procedure requiring a clean bowel.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Bulgaria, the Czech Republic, Germany, Denmark, Spain, Finland, France, Croatia, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and the Slovak Republic as Concerned Member States (CMS). The application was submitted under Article 10(b) of Directive 2001/83/EC, as amended, applicable for a fixed combination product of known active substances.

Plenvu contains the active ingredients macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride. Plenvu is a novel combination product developed for bowel clearance. It is formulated as a split-dosing formulation containing two osmotically-active powders for reconstitution; one containing polyethylene glycol (PEG or macrogol) 3350 and sodium sulfate, and the second containing ascorbate components (sodium ascorbate with ascorbic acid (vitamin C)) combined with a lower amount of macrogol 3350. Both doses contain electrolytes, sweetener and flavouring.

The composition of the powders is presented as three sachets contained in a clear secondary overwrap within a cardboard carton, and comprise a single treatment of Plenvu. Dose 1 contains 115.96 g of powder, Dose 2 Sachet A contains 46.26 g of powder and Dose 2 Sachet B contains 55.65 g of powder.

The doses are each reconstituted with 500 mL water to produce palatable oral solutions and administered in a split-dosing regimen either where one solution is given in the evening and the other in the morning prior to the clinical procedure, or where the two solutions are both given on the same day but about 1 to 2 hours apart.

Such dosing results in a total oral administration of PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride, and potassium chloride at approximately 2000, 687, 129, 108, 74, and 31 mg/kg body weight (BW), respectively, for a 70 kg adult. Plenvu is not recommended for use in children below 18 years of age.

The composition of Plenvu is based on the applicant’s experience with PEG-based laxatives, including Movicol (PL 00322/0070) marketed by the applicant, Norgine Limited, in the UK since December 1995, and the bowel preparation Moviprep (PL 20142/0005), also marketed by the applicant since January 2006. The applications cross-reference to non-clinical and clinical data provided for the existing marketing authorisations (MA) for Movicol and Moviprep, although no new non-clinical studies have been conducted to support this application for Plenvu. Moviprep also contains the following ingredients as in Plenvu, however at different quantities: PEG 3350, sodium sulfate, sodium ascorbate, ascorbic acid and electrolytes.

The oral administration of macrogol-based electrolyte solutions causes moderate diarrhoea and results in rapid emptying of the colon.

Macrogol 3350, sodium sulfate and high doses of ascorbic acid exert an osmotic action in the gut, which induces a laxative effect.

Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways.
The physiological consequence is a propulsive colonic transportation of the softened stools.

The electrolytes present in the formulation and the supplementary clear liquid intake are included to prevent clinically significant variations of sodium, potassium or water, and thus reduce dehydration risk.

The clinical development programme for this application consisted of one Phase I study, one Phase II study and three Phase III studies. These studies are discussed in more detail in the ‘IV, Clinical Aspects’ section of this report.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 27 September 2017. After a subsequent national phase, a licence was granted in the UK on 23 October 2017.
II QUALITY ASPECTS

II.1 Introduction
The ingredients of Plenvu are contained in three separate sachets. The first dose is supplied in one sachet
and the second dose is supplied in two sachets, A and B.

Dose 1 sachet contains the following active substances:
Macrogol 3350 100 g
Sodium sulfate anhydrous 9 g
Sodium chloride 2 g
Potassium chloride 1 g

The concentration of electrolyte ions when the first dose is made up to 500 ml of solution is as follows:
Sodium 160.9 mmol/500 ml
Sulfate 63.4 mmol/500 ml
Chloride 47.6 mmol/500 ml
Potassium 13.3 mmol/500 ml

Dose 2 (Sachets A and B) contains the following active substances:
Sachet A:
Macrogol 3350 40 g
Sodium chloride 3.2 g
Potassium chloride 1.2 g

Sachet B:
Sodium ascorbate 48.11 g
Ascorbic acid 7.54 g

The concentration of electrolyte ions when the second dose (Sachets A and B) is made up to 500 ml of
solution is as follows:
Sodium 297.6 mmol/500 ml
Ascorbate 285.7 mmol/500 ml
Chloride 70.9 mmol/500 ml
Potassium 16.1 mmol/500 ml

Other ingredients consist of the following pharmaceutical excipients sucralose (E955), aspartame
(E951), encapsulated citric acid [containing citric acid (E330) and maltodextrin (E1400)], mango flavour
[containing glycerol (E422), flavouring preparations, gum acacia (E414), maltodextrin (E1400) and
nature identical flavouring substances] and fruit punch flavour [containing flavouring preparations, gum
acacia (E414), maltodextrin (E1400) and nature identical flavouring substances].

The finished product is packed into three sachets. Each sachet comprises a laminate with the following
materials of construction: polyethylene terephthalate (PET), polyethylene, aluminium and extrusion
resin.

Dose 1 contains 115.96 g of powder, Dose 2 Sachet A contains 46.26 g of powder and Dose 2 Sachet B
contains 55.65 g of powder.

The three sachets are contained in a clear secondary overwrap within a cardboard carton, and comprise a
single treatment of Plenvu. The cardboard carton also contains the patient information leaflet.
Plenvu is available in packs containing 1 treatment and in packs containing 40, 80, 160 and 320 treatments. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substances
(1) Macrogol 3350
INN: Macrogols
Mixtures of polymers with the general formula H-[OCH₂-CH₂]ₙ-OH where n represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

Appearance: White or almost white solid with a waxy or paraffin-like appearance
Solubility: Very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils

Macrogol 3350 is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance macrogol 3350 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

(2) Sodium ascorbate
INN: Sodium ascorbate
Structure:

Molecular formula: C₆H₇NaO₆
Molecular weight: 198.1g/mol
Appearance: White or yellowish, crystalline powder or crystals.
Solubility: Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

Sodium ascorbate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance sodium ascorbate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

(3) Sodium sulfate, anhydrous
INN: Sodium sulfate, anhydrous
Molecular formula: Na₂SO₄
Molecular weight: 142.0/mol

Sodium sulfate anhydrous is the subject of a European Pharmacopoeia monograph.
Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

(4) Ascorbic acid
INN: Ascorbic acid
Structure:

Molecular formula: C6H8O6
Molecular weight: 176.1g/mol
Appearance: White or almost white, crystalline powder or colourless crystals, becoming discoloured on exposure to air and moisture.
Solubility: Freely soluble in water, sparingly soluble in ethanol (96 per cent).

Ascorbic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance ascorbic acid are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

(5) Sodium chloride
INN: Sodium chloride
Molecular formula: NaCl
Molecular weight: 58.44g/mol
Appearance: White or almost white, crystalline powder or colourless crystals or white or almost white pearls.
Solubility: Freely soluble in water, practically insoluble in anhydrous ethanol.
Sodium chloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance sodium chloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

(6) Potassium chloride

INN: Potassium chloride
Molecular formula: KCl
Molecular weight: 74.6g/mol
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Freely soluble in water, practically insoluble in anhydrous ethanol.

Potassium chloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance potassium chloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, powder for oral solution to provide a bowel cleansing product that is in a smaller volume and is more palatable than the existing products on the market which may require taking 4 litres of fluid. A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of citric acid and the mango and fruit punch flavours which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a
shelf-life of 2 years for the unopened sachets with the storage conditions ‘Store below 30°C.’ The shelf-life for the reconstituted solutions is 6 hours with the storage conditions ‘Keep prepared solutions below 25°C and drink it within 6 hours. The solutions may be stored in a refrigerator. The solutions must be covered. Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.’

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-ClinICAL ASPECTS

III.1 Introduction
The pharmacological, pharmacokinetic and toxicological properties of macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride are well known. As these six active substances are well known, no further studies are required and the applicant has provided none. The applicant has provided a summary to support this application, the summary discusses the non-clinical data provided for the existing MAs for Movicol and Moviprep, although no new non-clinical studies have been conducted to support this application for Plenvu.

The MAH’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology, III.3 Pharmacokinetics and III.4 Toxicology
The applicant has conducted a good laboratory practice (GLP) safety pharmacology study and a range of current GLP toxicology studies for Movicol as detailed below:

- single oral dose rat diuresis and saluresis study.
- 7-day and 3-month oral rat toxicity studies
- range-finding and 3-month oral dog toxicity studies
- bacterial reverse mutation assay (Ames) test, in vitro mouse lymphoma assay and in vivo mouse micronucleus test
- rat fertility, rat and rabbit embryo-fetal and rat pre- and post-natal studies

In addition, the applicant has conducted fourteen-day GLP oral rat and dog toxicity studies with Moviprep.

This non-clinical study data has additionally been supplemented with literature to support each component of the drug product.

Macrogol 3350 or PEG 3350:
PEGs are liquid or solid polymers with a large number of non-proprietary names and synonyms including Carbowax and macrogol. The general formula: \( HO \ CH_2-(CH_2-O-CH_2)m-CH_2OH \) may be used for PEGs, where “m” represents the average number of oxyethylene groups (the m value for PEG 3350 is 75.7 and for PEG 4000 is 69.0-84.0).

Medicinally, PEGs are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations). This use includes water-soluble bases for topical preparations and suppositories, as solvents, vehicles, solubilising agents, tablet binders, plasticizers in film coating and tablet lubricants.

Repeat dose toxicity studies in rats and dogs of 2 weeks duration showed that huge oral doses (in the high g/kg range) of the PEG-based electrolyte product Moviprep were well tolerated, with NOAELs of 10000 and 20000 mg/kg, respectively, established. Repeat dose toxicity studies in rats and dogs with the PEG-based electrolyte drug Movicol (for constipation), for up to 3 months duration, showed that huge oral doses (in the high g/kg range) were well tolerated, with a NOAEL of 10000 mg/kg established for both species. It is expected that considerable amount of material is non-absorbable and thus represent low toxicity.

The Movicol preparation demonstrated no evidence of genotoxicity in a modern battery of 2 in vitro and 1 in vivo test, and showed no evidence of embryotoxic or teratogenic properties following a full battery of reproduction toxicology studies. Minor effects on fetuses in the rat and rabbit embryo-fetal studies, (including reduced fetal weights and associated increased incidence of skeletal variations/retardations
and incomplete ossifications), were considered to be due to the exaggerated pharmacodynamic maternal effects of Movicol acting as an osmotic agent and impairing nutrition intake.

**Sodium ascorbate/ascorbic acid:**
Ascorbic acid was shown to be well tolerated in rodents in high g/kg levels, with no obvious target organ toxicity identified. No obvious correlation to the diarrhoea and other gastrointestinal disturbances reported from use of large doses in humans was seen. The increased urinary oxalate seen following repeated daily high doses in rats was not associated with renal calcium oxalate calculi and whilst large doses of ascorbic acid may result in hyperoxaluria in man, this has not consistently been correlated to clinical cases of renal calcium oxalate calculi formation. The occurrence of hyperoxaluria and/or renal calcium oxalate calculi are also not envisaged due to infrequent single exposures to ascorbic acid/sodium ascorbate expected from the expected clinical use of Plenvu. Ascorbic acid was shown to be non-genotoxic *in vivo*, and is not carcinogenic or toxic to reproduction.

**Sodium sulfate:**
Limited data showed no evidence of systemic toxicity from oral use of sodium sulfate and only occasional high dose cases of diarrhoea and/or dehydration were found. There was no obvious correlate to the abdominal cramps associated with clinical use of high doses of sodium sulfate to induce diarrhoea. No evidence of reproductive toxicity or genotoxicity was found.

**Sodium chloride:**
The proposed use of sodium chloride in Plenvu is at a level seen from its intake as a normal constituent of the diet and so no toxic effects can be expected.

**Potassium chloride:**
The proposed use of potassium chloride in Plenvu is at a level seen from its intake as a normal constituent of the diet and so no toxic effects can be expected.

All excipients have good safety profiles and additional information is included in the summary of product characteristics (SmPC) and product labelling which adequately addresses any concerns over toxicity. No concerns are raised in respect of impurities in the drug substance or drug product.

III.5 **Ecotoxicity/environmental risk assessment (ERA)**
The applicant has conducted an ERA for macrogol 3350 (PEG 3350), one of the active ingredients of Plenvu. The other active constituents of Plenvu, including sodium ascorbate/ascorbic acid, sodium sulphate, potassium chloride and sodium chloride, are negligible from an environmental risk assessment perspective.

This application represents a change in composition of components of other macrogol based pharmaceuticals, i.e. Moviprep/Movicol. As with other macrogol combinations emphasis has been on the macrogol 3350 component and this is presented again for Plenvu.

The applicant has provided an assessment of the environmental risk for macrogol 3350. PEC_{surface water} was 700 µg/L for macrogol 3350, this is above the action limit of 0.01 µg/L. The Phase II Tier assessment concluded that macrogol 3350 is not likely to be a risk to surface water, groundwater, to micro-organisms or be a risk to terrestrial plants and organisms. The ERA is complete and is acceptable.

III.6 **Discussion on the non-clinical aspects**
There are no objections to the approval of this application from a non-clinical viewpoint.
**IV. CLINICAL ASPECTS**

**IV.1 Introduction**

The clinical development programme for Plenvu consisted of one Phase I study, one Phase II study and three Phase III studies. These studies are summarised in the table below.

Plenvu may be referred to as NER1006 throughout this clinical aspects section of the report.

<table>
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<th>Phase/Study identifier</th>
<th>Objectives</th>
<th>Study design and type of control</th>
<th>Test/comparator product; dosage regimen; route of administration</th>
<th>Study subjects</th>
<th>Treatment duration</th>
</tr>
</thead>
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<tr>
<td>Phase I (PD and PK) NER1006-01/2011 (OUT) NCT01834742; EudraCT 2011-000271-14 (Romania) Module 5.3.4.1</td>
<td>To investigate PD, PK, and safety of various modified low volume PEG 3350 and ascorbic acid/ascorbate (PEG-ASC)-based gut cleansing solutions.</td>
<td>Open-label, randomised, single centre study with two Parts (A and B); active comparator drug: MOVIPREP®</td>
<td>Part A: NER1006 prototypes: three variable evening doses reconstituted with water up to 750 mL each and fixed morning dose reconstituted with water up to 500 mL, Oral MOVIPREP®; fixed evening and fixed morning doses; Powder for oral solution, reconstituted with water up to 1 L. Part B: NER1006 prototypes: Fixed evening dose and four variable morning doses; reconstituted each with water up to 500 mL. All Products: 2-Day split-dosing regimen: in the evening of Day 1 (day before colonoscopy) and in the morning of Day 2.</td>
<td>Healthy subjects Part A: 81 Part B: 80 18-45 years of age</td>
<td>2 days + 2 days follow-up (4 days total)</td>
</tr>
<tr>
<td>Phase II (PD and clinical results) NER1006-02/2012 (OPT)</td>
<td>Part A: To investigate PD, safety and tolerability of dose and taste optimized, low volume PEG/ASC-based formulations in healthy subjects. Part B: To investigate clinical efficacy, PD, PK, safety and tolerability in screening colonoscopy patients.</td>
<td>Open-label, randomised, single centre study with two Parts (A and B); active comparator drug: MOVIPREP®</td>
<td>Part A: NER1006: Various permutations of evening and morning doses; Reconstituted in 500-750 mL water; Oral MOVIPREP®; fixed evening and fixed morning doses; Powder for oral solution, reconstituted with water up to 1 L. Part B: NER1006: Variations of Part A-selected regimen OPT03: Reconstituted in 500 mL water; oral MOVIPREP®; same as Part A Both products: 2-Day split-dosing regimen: in the evening of Day 1 (before colonoscopy) and in the morning of Day 2.</td>
<td>Healthy subjects Part A: 117 40-70 years of age Part B: 120 Subjects undergoing screening colonoscopy; 55-70 years or 40-70 years of age if known risk of colon neoplasia</td>
<td>2 days</td>
</tr>
<tr>
<td>Phase III (efficacy and safety) NER1006-01/2014 (NOCT)</td>
<td>To evaluate the overall bowel cleansing efficacy and the “Excellent plus Good” cleansing rate in the colon ascendens of a 2-day split-dosing regimen with NER1006 vs. Trisulfate, graded using the HCS.</td>
<td>Randomised, parallel group, active comparator drug: Trisulfate bowel cleansing solution (SUPREP®)</td>
<td>NER1006: NER1006: Powder for oral solution, reconstituted with water up to 16 fl oz. (approx. 500 mL); two doses Trisulfate: 6 fl oz bottle of oral solution, mixed with water to make 16 fl oz (~ 500 mL) solution; two doses Both products: 2-day split-dosing regimen: first dose in the evening of the day before colonoscopy; second dose in the morning of the day of colonoscopy.</td>
<td>621 subjects undergoing screening, surveillance, or diagnostic colonoscopy.</td>
<td>2 days</td>
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</table>
IV.2 Pharmacokinetic studies

The OUT study had 2 parts (Part A compared various different evening formulations and Part B compared various morning formulations) with 81 healthy subjects in Part A (FAS) discussed below. Due to organisational considerations regarding the laboratory analyses, the pharmacokinetic profile was only evaluated for selected NER1006 prototypes E3/M3 and E3/M1 (E=evening/M=morning), and Moviprep, and therefore data from only 61 subjects were analysed. E3/M3 is most closely representative of the final Plenvu formulation. The pharmacokinetics of key active ingredients (PEG 3350, sulfate, ascorbic acid/sodium ascorbate, and electrolytes [sodium, potassium, chloride]) in blood, urine and stool at defined time points were evaluated.

The low concentrations and rapid clearance of PEG 3350 in blood (Table A) indicated that only small amounts of PEG 3350 passed into the blood and were then eliminated quickly. The major part of the ingested PEG 3350 stayed in the gastrointestinal tract and was excreted via faeces. The analyses of faeces samples demonstrated that in all three groups, the main part of the ingested PEG 3350 was excreted with the stool within three days after intake.

Table A Pharmacokinetic Parameters for PEG 3350 in Blood - OUT Study

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Mean (SD)</th>
<th>E3/M3 (N=21)</th>
<th>MOVIPREP® (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-tlast), [µg/mL*h]</td>
<td>17.3 (7.19)</td>
<td>16.5 (5.61)</td>
<td></td>
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<tr>
<td>tmax, [h]</td>
<td>3.0 (0.61)</td>
<td>3.8 (3.16)</td>
<td></td>
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<tr>
<td>Cmax, [µg/mL]</td>
<td>2.71 (1.170)</td>
<td>1.74 (0.580)</td>
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</tbody>
</table>
Assessor’s comments:
The above results were consistent with earlier findings on PEG gut cleansing solutions, which indicated that the major part of the PEG remains in the gastrointestinal tract and is eliminated in the stool, and that it is absorbed into the blood in only very low quantities and almost entirely excreted unchanged via the urine. Similarly, only very minor amounts of sulfate, ascorbic acid, and electrolytes [sodium, potassium, chloride] were absorbed.

**Study NER1006-01/2012 (OPT)**
The OPT study had two parts: Part A in healthy subjects and Part B in colorectal cancer screening population undergoing a colonoscopy, during which the bowel cleansing efficacy of the various formulations and pharmacokinetics were evaluated. Part B included three NER1006 groups (OPT003, OPT006, and OPT007) with different combinations of evening and morning doses and included 119 subjects (FAS).

The mean amount of PEG 3350 eliminated in faeces varied across groups by interval, but was comparable for Day 1 (0-8 hour interval) (Table B). As expected, due to the higher composition of PEG 3350 in Moviprep there were greater amounts of PEG in faeces for the Moviprep for the combined Days 1 and 2 (0-24 hour interval).

<table>
<thead>
<tr>
<th>Interval</th>
<th>Arithmetic mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPT003 (N=29)</td>
</tr>
<tr>
<td></td>
<td>OPT007 (N=30)</td>
</tr>
<tr>
<td></td>
<td>OPT006 (N=30)</td>
</tr>
<tr>
<td></td>
<td>MOVIPREP* (N=30)</td>
</tr>
<tr>
<td>0-8 h</td>
<td>62.7 (24.05)</td>
</tr>
<tr>
<td>0-12 h</td>
<td>66.5 (23.20)</td>
</tr>
<tr>
<td>0-24 h</td>
<td>122.9 (18.85)</td>
</tr>
<tr>
<td>12-24 h</td>
<td>56.4 (22.76)</td>
</tr>
</tbody>
</table>


**Table B: PEG 3350 Amount (g) Eliminated in Faeces-OPT study**

Assessor’s Comment
The pharmacokinetic profiles of the different formulations were largely similar. The components (especially the ascorbate) were not absorbed into the circulation in amounts of any clinical concern but were instead excreted primarily in the faeces.

**Conclusion on pharmacokinetic studies**
There were no major differences in pharmacokinetic profiles of the different prototype formulations, other than those attributable to the differences in amounts and distribution of osmotically active components across the two doses for each of the formulations tested.

**IV.3 Pharmacodynamic studies**

**General principles**
PEG 3350 principally exerts an osmotic effect within the lumen of the gastrointestinal tract, and is absorbed in insufficient quantity to demonstrate systemic effects. The combination of PEG 3350 with balanced electrolytes amplifies the osmotic gradient and prevents undue net electrolyte loss or gain. This osmotic effect is established and maintained with a pressure gradient across intestinal mucosal cell membranes, thereby inhibiting water absorption from the intestinal lumen and adding bulk to the colonic contents. In addition, an effective propulsive colonic motility and/or facilitation of defecation is established by metabolic and pharmacological pathways restoring the required intrinsic entero-enteric
reflexes and propulsive motility via stimulation of myenteric and mucosal intrinsic primary afferent neurons. The latter are highly sensitive mechanoreceptors that are stimulated by the changes in stool bulk and composition.

Only limited absorption of ascorbic acid takes place during oral ingestion. Ascorbic acid has conventional osmotic properties and therefore exerts a predictable osmotic laxative effect based only on its physical chemistry. It is normal practice to correct the exchange of bicarbonate for chloride in the distal colon by adding sodium bicarbonate to colonic lavage solutions. Since bicarbonate is incompatible with ascorbic acid in aqueous solution, the same effect is achieved in Plenvu oral solution by replacing part of the ascorbic acid with sodium ascorbate. This corrects the base deficit while exerting an equivalent osmotic effect to ascorbic acid.

The sodium sulfate in Plenvu oral solution also contributes to the osmotic effect of the product, since sulfate is a poorly absorbed anion which prevents the absorption of an equivalent amount of sodium (i.e., two sodium ions for each divalent sulfate ion). It is believed to exert no other PD action.

**Study NER1006-01/2011(OUT)**

The OUT study had two parts (Part A compared various different evening formulations and Part B compared various morning formulations), during which the PD effects (stool weight) of various modified low volume PEG + ascorbate gut cleansing solutions were evaluated in healthy subjects. There were 81 healthy subjects in Part A (FAS) and 80 in Part B (FAS). There were no clinically relevant differences in the demographics between the groups in Parts A or B.

The primary variable in this study was the stool weight output from the start of the intake to 24 hour after with an output of around 3000 g as the preferred goal. Only the E3 solution (together with M3) gave a stool weight of more than the target weight of 3000 g, supporting the selection of E3 as the standard evening dose for Part B of the study (Table C). In Part B, only the combination of E3 with the morning solution M1 achieved the target weight of 3000 g.

**Table C: Summary Statistics for Stool Weights-OUT Study**

<table>
<thead>
<tr>
<th></th>
<th>E2/M3 (N=19)</th>
<th>E3/M3 (N=19)</th>
<th>E-IP/M3 (N=18)</th>
<th>MOVITREX® (E and M) (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of stool weight [g] (Median [Q1; Q3])</td>
<td>2981.30 [2741.55; 3435.55]</td>
<td>3493.20 [2982.40; 3804.30]</td>
<td>2796.80 [2641.00; 3296.25]</td>
<td>3145.95 [2643.95; 3280.65]</td>
</tr>
</tbody>
</table>

**Study NER1006-01/2012(OPT)**

The OPT study had two parts: Part A in healthy subjects and Part B in a colorectal cancer screening population undergoing a colonoscopy, during which the bowel cleansing efficacy of the various
formulations was evaluated. The formulations were adaptations of those selected from the OUT study, in that they were taste and flavour-optimized in an attempt to reduce the relatively high prevalence of nausea and vomiting observed from the OUT study with the aim to improve the tolerability profile. Part A included three NER1006 groups (OPT001, OPT002, and OPT003) with different combinations of evening and morning doses and Part B included three treatment groups of NER1006 (OPT003, OPT006, and OPT007) with different combinations of evening and morning doses and additional intake of specified volumes of clear fluid. All regimens had a total mandated fluid intake of 3 L, except for OPT007 which had a mandated fluid intake of 2 L. All subjects could take additional fluids ad libitum. Regimen OPT002 was a reversal of the order of doses in OPT001. Regimen OPT006 was the same as OPT003 with reduced ascorbate in Dose 2.

There were 119 subjects in Part A (FAS) and 120 in Part B (FAS). There were no clinically relevant differences in demographics between the groups in Parts A or B.

In Part A, OPT002 and OPT003 met the requirements for mean stool weight >2750 g with a calculated p-value <0.1, and a lower boundary of 90% CI >2750 g and greater than that of the reference (OPT004, Moviprep). Since the OPT003 regimen gave the highest stool weight with comparable safety, it was chosen for Part B. In Part B, only OPT003 and OPT007 met the requirement of stool weight of >2750 g (Table D).

### Table D: Summary Statistics for Stool Weights-OPT Study

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPT001</td>
<td>OPT002</td>
</tr>
<tr>
<td>Mean (SD) [g]</td>
<td>2951.0 (873.77)</td>
<td>3218.7 (809.89)</td>
</tr>
<tr>
<td>Median (range) [g]</td>
<td>2978.75 (729.2-4328.5)</td>
<td>3326.20 (912.0-4559.1)</td>
</tr>
<tr>
<td>[90% CI]</td>
<td>[2679.99; 3222.10]</td>
<td>[2962.85; 3474.52]</td>
</tr>
<tr>
<td>p-value</td>
<td>0.2176</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

CI = confidence interval; N = number of subjects with data; SD = standard deviation.

Assessor’s Comment

The overall stool weight output during the 24 hour period was statistically significantly higher than the pre-defined goal of 2750 g only for groups OPT002 and OPT003 in Part A and OPT003 and OPT007 in Part B. Stool output peaked at 2-3 hours after each dose, returning to low levels by 5-6 hours after intake. The percentage of subjects who reached clear effluent was higher (≥80%) in groups OPT003 and OPT007 compared to all other groups.
The biological activity of the individual osmotically active components in each was such that the components were largely excreted in the faeces, where they contributed to the faecal load, and to a small extent in the urine. Overall, there were no major differences in pharmacokinetic profiles of the different formulations, other than those attributable to the differences in amounts and distribution of osmotically active components across the two doses for each of the formulations tested.

IV.4 Clinical efficacy
Evaluation of efficacy
Successful colonoscopy is ultimately determined by the ability to visualise the entire colonic mucosa in order to see any lesions that may be present. Full visualisation of the colon mucosa is achieved through use of an effective bowel preparation. Therefore, in the context of bowel preparations, such as NER1006, “clinical efficacy” is synonymous with “bowel cleansing efficacy” which is the primary clinically meaningful endpoint.

Cleansing efficacy of bowel preparations is typically assessed using a scale to measure cleansing, which, for the preparation to be deemed to be effective, requires visualisation of the colon mucosa. Over the years a number of different cleansing scales have been developed. In the NER1006 Phase II and III programme, Norgine used the Harefield Cleansing Scale (HCS), a rigorous scale that objectively evaluates the entire length of the colon in a stepwise manner in order to arrive at a final cleansing grade. The HCS was developed between 1998 and 2002 and validated in 2009/2010 (Halphen 2013). The description of each score within the scale is simple and easily interpreted. This scale was used to demonstrate efficacy in the Moviprep EU Marketing Authorisation Applications (MAAs). It requires the colonoscopist to make a separate evaluation (scoring) of the cleansing observed in each of five colon segments (colon ascendens, colon transversum, colon descendens, colon sigmoideum, and rectum) and is performed during withdrawal of the colonoscope. All bowel cleansing scales are developed for clinical practice, and most (specific in Boston Bowel Preparation Scale [BBPS], not explicit in Aronchik or Ottawa scales) score upon withdrawal because it is only during withdrawal, after having reached the caecum that one can be certain of the location of the tip of the scope (through which the visualisation is done) using the landmarks within the colon. However, to ensure that no bias toward non-inferiority was introduced (e.g., from additional flushing/suctioning occurring during scope insertion), and at the request of the FDA, a post-hoc sensitivity analysis was performed to compare the scoring on insertion to that during withdrawal.

In the HCS, each segment is scored on a 5-point scale from 0 to 4, and thereafter an overall grade of A through to D is assigned, whereby A and B represent cleansing success and C and D represent cleansing failure (Table E). In summary, and in contrast to other scales where there is a less objective measure of success, for cleansing to be successful according to the HCS, every segment of the colon must be free of stool/liquid and/or any remaining debris should be easily removable allowing full visualisation of the colon mucosa.
Table E: Description of Colonic Cleansing Assessment using Harefield Cleansing Scale

<table>
<thead>
<tr>
<th>Segment Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Irremovable, heavy, hard stools</td>
</tr>
<tr>
<td>1</td>
<td>Semi-solid, only partially removable stools</td>
</tr>
<tr>
<td>2</td>
<td>Brown liquid/removable semi-solid stools</td>
</tr>
<tr>
<td>3</td>
<td>Clear liquid</td>
</tr>
<tr>
<td>4</td>
<td>Empty and clean</td>
</tr>
</tbody>
</table>

Note: Scores of 2, 3, and 4 corresponded to success scores. Grades of A and B corresponded to success grades.

The HCS was used across all three Phase III studies for consistency.

Summary of the main efficacy results

The main Phase III analysis population was the modified Full Analysis Set (mFAS) for this submission and was used in the analyses of all study variables. The mFAS consisted of all randomised patients with the exception of any patient who (i) was randomised but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug. Sensitivity analyses of primary endpoint data were also performed using the FAS and the Per Protocol (PP) set.

For the NOCT study, of the total 621 FAS patients, 310 were included in the NER1006 group and 311 in the Trisulfate group. Of these 255 patients (82.3%) in the NER1006 and 261 patients (83.9%) in the Trisulfate groups completed the study. The most frequently reported reasons for discontinuation were “other” reasons (about 9-10%) and withdrawal of patient (about 4-5%). Of the total 621 FAS patients, 556 patients (89.5%) were included in the mFAS (NER1006: 276 patients; Trisulfate: 280 patients).

For the MORA study, of the total 849 FAS patients, 283 patients each were included in the NER1006 2-Day and 1-Day groups and in the Moviprep group. Of these, 260 patients (91.9%) in the NER1006 2-Day, 262 patients (92.6%) in the NER1006 1-Day, and 259 patients (91.5%) in the Moviprep groups completed the study. The most frequently reported reasons for discontinuation were withdrawal of patient (about 3-4%) and “other” reasons (about 2-3%). Of the total 849 FAS patients, 822 patients (96.8%) were included in the mFAS (NER1006 2-Day: 275 patients; NER1006 1-Day: 275 patients; Moviprep: 272 patients).

For the DAYB study, of the total 515 FAS patients, 258 were included in the NER1006 group and 257 in the SP+MS group. Of these, 233 patients (90.3%) in the NER1006 and 240 patients (93.4%) in the SP+MS groups completed the study. The most frequently reported reason for discontinuation was withdrawal of patient (about 4-6%). Of the total 515 FAS patients, 501 patients (97.3%) were included in the mFAS (NER1006: 250 patients; SP+MS: 251 patients).
For the Phase II OPT study, there were 30 patients randomised to each of the treatment groups in Part B, three groups with different dosing regimens of NER1006 and one active comparator (Moviprep). The demographics and baseline characteristics were balanced across all treatment groups for all submission studies.

**Primary Efficacy Endpoints**

Results for the alternative primary endpoint 1, overall bowel cleansing quality using the HCS, demonstrated the non-inferiority of NER1006 to the active comparators Trisulfate, Moviprep and SP+MS, in all three studies although superiority was not demonstrated (Table E, Figure 2, Figure 3, Figure 4). In contrast, although non-inferiority was also demonstrated in all studies for the alternative primary endpoint 2, “Excellent plus Good” bowel cleansing rate in the colon ascendens, in the MORA study, both NER1006 2-Day and 1-Day (Morning) groups had cleansing rates of “Excellent plus Good” more than double that of the active comparator (Moviprep) and superiority was demonstrated (Table E, Figure 3). Note: due to the inclusion in the mFAS of small numbers of patients for whom colonoscopy was not performed and missing primary endpoint data were imputed as zero, including a few cases where eligibility could not be confirmed, the efficacy results described here are conservative estimates; had such patients not been included, the efficacy rates may have been higher. Successful bowel cleansing in the overall bowel and the colon ascendans was lower in the DAYB study compared to NOCT or MORA. This may be related to the longer time between administration of the bowel prep and the colonoscopy in the DAYB study.

**Table E: Alternative primary Endpoints 1 and 2 (Harefield Cleansing Scale)-NOCT, MORA and DAYB Studies**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOCT</td>
</tr>
<tr>
<td>NER1006</td>
<td>Trisulfate</td>
</tr>
<tr>
<td>2-Day</td>
<td>(N=276)</td>
</tr>
<tr>
<td>Primary Endpoint 1: Overall Bowel Cleansing Quality</td>
<td></td>
</tr>
<tr>
<td>HCS Success(^a)</td>
<td>235 (85.1)</td>
</tr>
<tr>
<td>Primary Endpoint 2: High Quality Cleansing Rate in the Colon Ascendens</td>
<td></td>
</tr>
<tr>
<td>HCS Excellent plus Good(^b)</td>
<td>99 (35.9)</td>
</tr>
</tbody>
</table>

HCS = Harefield Cleansing Scale; N = total number of patients;
\(^a\) Grades A and B are classified as successful cleansing and Grades C and D are classified as failures.
\(^b\) Score of 4 corresponded to excellent cleansing. Score of 3 to good cleansing, score of 2 to adequate cleansing, and scores of 1 and 0 to failure in cleansing.
Figure 2  Primary and Key Secondary Endpoints - NOCT Study

- HCS
  - Overall Success Rate
  - Success Rate in Colon Ascendens

- ADR
  - Colon Ascendens
  - Overall

- PDR
  - Colon Ascendens
  - Overall

ADR = adenoma detection rate; HCS = Hartrefield Cleansing Scale, PDR = polypl detection rate.

Figure 3  Primary and Key Secondary Endpoints - MORA Study

(A) MOVIPREP® and NER1006 2-Day Comparison
Sensitivity analyses of the alternative primary endpoint data using the FAS and the PP sets were consistent with the findings on the mFAS. Furthermore, in the MORA study, superiority of cleansing in the overall colon was demonstrated statistically for NER1006 2-Day group in the PP set (1-sided p-value 0.014) and superiority of cleansing in the colon ascendens was also demonstrated statistically for NER1006 2-Day group and NER1006 1-Day group in the FAS and PP set (1-sided p-value was <0.001 for both groups in both sets). In the DAYB study, superiority of cleansing in the overall colon and in the
colon ascendens were also demonstrated statically for NER1006 group in the PP set (1-sided p-values of 0.023 and 0.015, respectively).

In all three studies, the percentage of patients with “Excellent plus Good” HCS scores across all colon segments was higher in the Plenvu treatment groups as compared with the respective comparator treatment groups.

In the Phase II OPT study Part B, bowel cleansing HCS scores assigned to the three NER1006 groups for all colon segment assessments were higher than the scores assigned to the reference group. For the three NER1006 groups, most subjects were assigned a final HCS grading of ‘A’ while most subjects in the reference group were assigned a final grading of ‘B’.

Assessor’s Comment
In terms of bowel cleansing efficacy of Plenvu oral solution was independent of whether cleansing was assessed during advancement or withdrawal. There was no meaningful difference in success rates between the two methods of assessment. Plenvu treatment was non-inferior to Trisulfate treatment for both alternative primary endpoints

Secondary Endpoints
There were no statistically significant differences in number and rates of adenomas or polyps detected in either the colon ascendens or the overall colon across treatment groups in all studies (95% CIs all contain 0), although in the MORA and DAYB studies, the highest rates of polyp detection in the colon ascendens were in the NER1006 groups: in MORA the rates were 23.3% in the NER1006 2-Day group and 16.5% in the Moviprep group, with superiority of NER1006 2-Day demonstrated statistically using the Fisher’s Exact Test (1-sided P value 0.024). Given the high level of cleansing in all treatment groups in the NOCT and MORA studies, the rates of lesions seen are probably a true reflection of the prevalence of lesions in these particular patient populations.

There were no relevant differences in success percentages of bowel cleansing using the BBPS in either the overall colon or the right colon across treatment groups in the NOCT study. However, in the MORA study, the highest success was in the NER1006 2-Day group for both the overall and right colon and the differences between both of the NER1006 groups (2-Day and 1-Day) compared to Moviprep were statistically significant (95% CIs do not contain 0). In the DAYB study, in the overall colon, cleansing success was achieved in 146 (58.4%) patients in the NER1006 treatment group and 115 (45.8%) patients in the SP+MS treatment group.

The overall compliance (patient took at least three quarters of each dose) according to the patient diary was high and comparable in both treatment groups (255 patients [92.4%] in the NER1006 group and 255 patients [91.1%] in the Trisulfate group) in the NOCT study with similar compliance for both doses of bowel preparation in both treatment groups. Similarly, compliance was high for all three treatment groups in the MORA study (>84%) and for both treatment groups in the DAYB study (>77%).

Conclusions on Efficacy
The results of the three pivotal studies with four NER1006 treatment groups and three treatment regimens clearly demonstrated the non-inferiority of NER1006 to the active comparators for a validated measure of bowel cleansing (the HCS), for the overall colon (first alternative primary endpoint). Non-inferiority was also demonstrated for a high level of cleansing (“Excellent plus Good” using the HCS scoring system) in the ascending colon/cecum (second alternative primary endpoint). Results from the subgroup analyses indicated no reasons to preclude use of NER1006 in different age groups on the basis of overall bowel cleansing efficacy.

In addition, superiority compared to an active comparator was demonstrated for “Excellent plus Good” cleansing in the ascending colon/cecum. This was demonstrated for two of the NER1006 groups (2-day
and 1-day split-dosing regimens in the MORA study), indicating the robustness of this finding. Although there was a positive difference over comparator in the NER1006 treatment arms in the NOCT and DAYB studies, superiority could not be demonstrated.

The efficacy of NER1006 was also supported with a number of secondary endpoints.

**IV.5 Clinical safety**

**Exposure**

NER1006 is a split-dosing regimen to be administered for bowel cleansing prior to any procedure that requires a clean bowel. In Phase III, 2-day split (10-12 hours apart) or 1-day split (1-2 hours apart) dosing regimens were used. For the 2-day split-dosing regimen, the first dose was administered on the evening prior to the colonoscopy (at approximately 18:00) and the second was administered on the following morning prior to the colonoscopy at approximately 06:00. For the 1-day split-dosing regimen, the doses were administered 1-2 hours apart either on the day prior to the colonoscopy or the day of the colonoscopy.

To date, 1349 adult patients (aged 18-86 years) have been exposed to the different prototype and final formulations of NER1006: 231 were healthy subjects (OUT study [141 subjects] and Part A OPT study [90 subjects]) and 1118 subjects were age-appropriate screening, surveillance, or diagnostic colonoscopy patients from Part B of the OPT study (90 subjects) and the NOCT, MORA, and DAYB studies (1028 patients).

The only relevant patient groups excluded from the intended population by the study exclusion criteria were patients with severe heart failure (NYHA III and IV), liver disease (Child-Pugh Class B+C), severe renal disease, and ongoing severe acute inflammatory bowel disease, all of which will be reflected in the product label.

In Phase III, there were 524 patients who received the 2-day dosing regimen and 504 the 1-day dosing regimen. Each dose of NER1006 was 500 mL, followed by an additional 500 mL of clear fluid. Patients were allowed to take additional clear fluid ad libitum.

**Demographic Characteristics**

There were no relevant differences in demographic and background characteristics between patients treated with 1-Day and 2-Day split regimens in the combined NER1006 groups of the NOCT, MORA and DAYB studies or between the treatment groups in the individual studies. Most patients were 45-65 years old, with a higher proportion of patients <45 years old in the 1-Day group (21.2%) compared to the 2-Day group (12.4%). In both groups, the majority of patients were White and a marginally higher proportion of patients were female (53.6% in the 2-Day group and 58.3% in the 1-Day group). About half of the patients in the NER1006 groups (2-Day group: 54.8%, 1-Day group: 50.8%) were undergoing a screening colonoscopy, with a higher proportion of patients in the 2-Day group having had previous bowel preparations (50.4%) than in the 1-Day group (30.0%). In the 2-Day group, concomitant medications that were more frequently used included general anaesthetics (74.4% of patients in the 2-Day group vs. 42.3% in the 1-Day group) and intravenous fluids (38.9% in the 2-Day group vs. 1.6% in the 1-Day group). In general, patients with intravenous fluids and were on general anaesthetics and most were in the NOCT study. Previous medical conditions were reported in a higher proportion of patients in the 2-Day group (65.8%) compared to the 1-Day group (48.8%). In both dosing groups, previous medical history was reported most frequently for the system organ class (SOC) of “Surgical and Medical Procedures” (53.2% in the 2-Day group and 35.7% in the 1-Day group).

Ongoing medical conditions were reported in 86.6% of patients in the 2-Day group and 77.2% of patients in 1-Day group. The most frequently reported SOCs for ongoing medical conditions (>30%) were “Gastrointestinal Disorders” (45.8% in the 2-Day group and 33.7% in the 1-Day group), “Vascular
Disorders” (38.9% in the 2-Day group and 34.7% in the 1-Day group), and “Metabolism and Nutrition Disorders” (34.0% in the 2-Day group and 22.4% in the 1-Day group). Despite these differences in ongoing medical history, the majority of patients (≥76%) in both groups did not have any of the current medical conditions of interest (i.e., diabetes, cardiac conditions, inflammatory bowel disease, and diverticular disease).

**Common Adverse Events**

As with all bowel cleansing agents, NER1006 induces watery diarrhoea as part of its intended outcome so this is not regarded as a side effect. Gastrointestinal symptoms (e.g., vomiting, nausea, and abdominal pain) are commonly observed AEs of bowel cleansing agents. These symptoms are expected as the usual symptoms for a bowel preparation prior to colonoscopy.

Overall, treatment-emergent adverse events (TEAEs) were reported in low percentages, but a higher proportion of patients in the NER1006 2-day split regimen (22.5%) compared to the NER1006 1-day split regimen (17.7%) (Table F). The majority of TEAEs in both regimens were considered mild by the investigator. A similar proportion of patients had TEAEs considered related to IMP in the NER1006 regimens (2-day split: 13.4% and 1-day split: 13.5%). There were very few TEAEs leading to treatment discontinuation (2 patients [0.4%] in 1-day split NER1006, both considered related). Very few serious TEAEs were reported in the NER1006 treatment regimens; and none of these serious TEAEs were considered related to IMP. No deaths were reported in any of the NER1006 treatment regimens.

**Table F: Summary of TEAEs-Combined Phase III Studies**

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Number (% of Patients)</th>
<th>2-Day (N=524)</th>
<th>1-Day (N=504)</th>
<th>Overall (N=1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one TEAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAEs related to IMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious TEAEs related to IMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAEs leading to discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAEs related to leading to discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMP = investigational medicinal product; N = number of patients; TEAE = treatment-emergent adverse event.
Notes: Related TEAEs were classified as TEAEs that were possibly or probably related to IMP. TEAEs that were missing a relationship were assumed to be “related”.

Across the NOCT, MORA, and DAYB studies, the majority of TEAEs were considered mild to moderate in severity by the investigator (Table G). No more than two patients (0.8% of patients) in any treatment group of any study experienced a serious TEAE. In general, the percentages of total TEAEs and TEAEs considered related to IMP were marginally higher in the NER1006 groups compared to the
active comparators. TEAEs leading to discontinuation of IMP were rare and did not occur in more than one patient in any treatment group.

Table G: Summary of TEAEs- NOCT, MORA and DAYB Studies

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>NOCT</th>
<th>Number (%) of patients</th>
<th>MORA</th>
<th>Number (%) of patients</th>
<th>MOVIPREP®</th>
<th>Number (%) of patients</th>
<th>DAYB</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NER1006 (N=262)</td>
<td>Trisulfate (N=265)</td>
<td>NER1006 2-Day (N=262)</td>
<td>NER1006 1-Day (N=269)</td>
<td>NER1006 MOVIPREP® (N=263)</td>
<td>NER1006 SP-MS (N=235)</td>
<td>SP-MS (N=241)</td>
<td></td>
</tr>
<tr>
<td>At least one TEAE</td>
<td>72 (27.5)</td>
<td>49 (18.5)</td>
<td>46 (17.6)</td>
<td>49 (18.2)</td>
<td>31 (11.8)</td>
<td>40 (17.0)</td>
<td>24 (10.0)</td>
<td></td>
</tr>
<tr>
<td>TEAEs related to IMP</td>
<td>39 (14.9)</td>
<td>25 (9.4)</td>
<td>31 (11.8)</td>
<td>40 (14.9)</td>
<td>20 (7.6)</td>
<td>28 (11.9)</td>
<td>10 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serious TEAEs related to IMP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild TEAEs</td>
<td>41 (15.6)</td>
<td>30 (11.3)</td>
<td>43 (16.4)</td>
<td>43 (16.0)</td>
<td>27 (10.3)</td>
<td>31 (13.2)</td>
<td>19 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Moderate TEAEs</td>
<td>27 (10.3)</td>
<td>16 (6.0)</td>
<td>1 (0.4)</td>
<td>5 (1.9)</td>
<td>4 (1.5)</td>
<td>5 (2.1)</td>
<td>4 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td>4 (1.5)</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>TEAEs leading to IMP discontinuation</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TEAEs related to IMP leading to discontinuation</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

IMP = investigational medicinal product; N = number of patients; SP-MS = sodium picosulfate + magnesium salt;
TEAE = treatment-emergent adverse event.

Note: Related TEAEs were classified as TEAEs that were possibly or probably related to IMP. TEAEs that were missing a relationship were assumed to be "related".
Table H: TEAEs by System Organ Class and Preferred Term- Combined Phase III Studies

<table>
<thead>
<tr>
<th>System organ class(^a)</th>
<th>Preferred term(^b)</th>
<th>Number (% of patients)</th>
<th>2-Day (N=524)</th>
<th>1-Day (N=504)</th>
<th>Overall (N=1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>73 (13.9)</td>
<td>59 (11.7)</td>
<td>132 (12.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>33 (6.3)</td>
<td>20 (4.0)</td>
<td>53 (5.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>3 (0.6)</td>
<td>9 (1.8)</td>
<td>12 (1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>3 (0.6)</td>
<td>5 (1.0)</td>
<td>8 (0.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal tenderness</td>
<td>7 (1.3)</td>
<td>0</td>
<td>7 (0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
<td>4 (0.8)</td>
<td>2 (0.4)</td>
<td>6 (0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain lower</td>
<td>0</td>
<td>4 (0.8)</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastritis</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhoids</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal discomfort</td>
<td>0</td>
<td>3 (0.6)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hiatus hernia</td>
<td>3 (0.6)</td>
<td>0</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate decreased</td>
<td>5 (1.0)</td>
<td>0</td>
<td>5 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>15 (2.9)</td>
<td>9 (1.8)</td>
<td>24 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>9 (1.7)</td>
<td>7 (1.4)</td>
<td>16 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>4 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar state</td>
<td>3 (0.6)</td>
<td>0</td>
<td>3 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (1.7)</td>
<td>6 (1.2)</td>
<td>15 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
<td>3 (0.6)</td>
<td>3 (0.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(N\) = number of patients; \(TEAE\) = treatment-emergent adverse event.

\(^a\) The cut off used is ≥0.5% of patients in any treatment group from system organ classes with ≥2.0% incidence in either treatment group.

As expected for patients taking a bowel preparation, the majority of TEAEs in both regimens was in the SOC of “Gastrointestinal Disorders” (2-Day group: 13.9% of patients; 1-Day group: 11.7% of patients), with vomiting and nausea being the most frequent preferred terms in both regimens (Table H).
Table I: Causally Related TEAEs by System Organ Class and Preferred Term- Combined Phase III Studies

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Number (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-Day (N=524)</td>
<td>1-Day (N=504)</td>
</tr>
<tr>
<td>Total related TEAEs</td>
<td>70 (13.4)</td>
<td>68 (13.5)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>51 (9.7)</td>
<td>50 (9.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (4.4)</td>
<td>28 (5.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (5.5)</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (0.4)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (0.6)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>0</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Investigations</td>
<td>11 (2.1)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Glomerular filtration rate decreased</td>
<td>3 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>13 (2.5)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>7 (1.3)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hyperosmolarstate</td>
<td>3 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

N = number of patients; TEAE = treatment-emergent adverse event.

\[\text{a: The cut off used is 20.5% of patients in any treatment group from system organ classes with 22.0% incidence in either treatment group.}\]

Note: Related TEAEs were classified as TEAEs that were possibly or probably related to IMP. TEAEs that were missing a relationship were assumed to be "related".

Conclusions on Safety

NER1006 was shown to have an acceptable safety profile and be well-tolerated in a large patient population of over 1000 patients undergoing screening, surveillance, or diagnostic colonoscopy. There were very few serious TEAEs (none of them were considered related to study medication) and no deaths in any of the studies.

Percentages of TEAEs were generally comparable between studies and treatment groups. Marginally higher rates for NER1006 compared to the active comparators were observed for some TEAEs (especially vomiting and nausea, mostly of mild severity) which are known to be related to the bowel cleansing preparations and were still well below the rates published in the literature for similar products.

Transient increases in sodium values from within to above the normal range in NER1006 patients rapidly returned to normal after the colonoscopy procedure and were more common in patients on general anaesthetic. This may have been due to insufficient hydration in these patients as these patients have restrictions on the amount of fluid they may consume prior to the procedure and does not appear to indicate any safety issue. Based on these data, there does not appear to be any unacceptable safety risk with the use of NER1006.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Plenvu.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Electrolytes disturbance</td>
</tr>
<tr>
<td></td>
<td>Transient increase in blood pressure</td>
</tr>
<tr>
<td></td>
<td>Transient increase in liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Allergic reactions (including anaphylaxis)</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Arrhythmias (including atrial fibrillation)</td>
</tr>
<tr>
<td></td>
<td>Perforation/aggravation of the condition in patients with toxic megacolon as a result of severe IBD</td>
</tr>
<tr>
<td></td>
<td>Aspiration in patients with diminished levels of consciousness/severely debilitated patients especially if prepared with a nasogastric tube</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in patients with glucose-6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td></td>
<td>Use in paediatric population</td>
</tr>
<tr>
<td></td>
<td>Use in pregnancy/lactation</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application from a clinical point of view.

V User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The application complies with CHMP guidance documents and contains an adequate study to support the application. There are no indications in the light of scientific knowledge that they differ significantly from the other similar medicinal products with regard to safety or efficacy. Plenvu contains the widely used and well-known active substances macrogol 3350, sodium ascorbate, sodium sulfate anhydrous, ascorbic acid, sodium chloride and potassium chloride which have a long history of established favourable risk-benefit profile.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
Dose 1

Instructions on Use:
Empty the contents of the Dose 1 sachet into a container, make up to 500 mL with water and stir until dissolved. Keep prepared solution below 25°C and drink it within 6 hours. The solution may be stored in a refrigerator. The solution must be covered.

Norgine BV,
Hogeheide 7, 1101 CA,
Amsterdam ZO, The Netherlands

10095902
F PL 20142/0020

See back of this packet for instructions for use.

Keep out of the sight and reach of children.

Prior to opening Store below 30°C
Read the package leaflet before use

Oral use

Potassium chloride 1 g, sodium sulfate anhydrous 9 g, sodium chloride 2 g

Dose 1 contains: Macrogol 3350 100 g
Dose 2 Sachet A contains: Macrogol 3350 40 g; Sodium chloride 3.2 g; Potassium chloride 1.2 g.

Oral use.
Read the package leaflet before use.
Prior to opening store below 30°C.

Keep out of the sight and reach of children.
Dose 2 Sachet A contains aspartame (E951).
Peel apart the two sachets. See back of this sachet for instructions for use.
Dose 2 Sachet B

Instructions on Use:

Empty the contents of Dose 2 Sachet B together with Dose 2 Sachet A into a container, make up to 500 mL with water and stir until dissolved. Keep prepared solution below 25°C and drink it within 6 hours. The solution may be stored in a refrigerator. The solution must be covered.

Norgine B.V.
Hoge Hilweg 7, 1101 CA
Amsterdam ZO, The Netherlands

10097121

PL 20142/0020

Dose 2 Sachet B contains: Sodium ascorbate 48.11 g; Ascorbic acid 7.54 g.

Dose 2 Sachet B 99%
### Annex 1 - Table of content of the PAR update for MRP and DCP

#### Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
   (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>