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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209381
Link to EDR	Application 209381 - Sequence 0033 - 0033 (35) 04/30/2018 TRIAGE-1 /Electronic Submission/Gateway
Submission Date	Original: 04/13/2017 (seq. No.0009, SDN 11) Reponse to IR: 11/17/2017 (SDN 25), 11/27/2017 (SDN 26), 03/05/2018 (SDN 29)
Submission Type	Original submission, 505(b)(2), Standard review
Brand Name	Plenvu
Generic Name	PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride and Potassium Chloride
Dosage Form and Strength	Powder for Oral Solution
Route of Administration	Oral Administration
Proposed Indication	Cleansing of the colon in preparation for colonoscopy
Applicant	Norgine
Associated IND	IND 120089
OCP Review Team	Dilara Jappar, Ph.D. (Clinical Pharmacology) Insook Kim, Ph.D. (Clinical Pharmacology Team Leader)
OCP Final Signatory	Michael Pacanowski, Pharm.D. (Acting DCP3 Division Director)

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1. EXECUTIVE SUMMARY

The Applicant has submitted a NDA for PLENVU (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride) for cleansing of the colon in preparation for colonoscopy in adults. PLENVU is an osmotic laxative consisting of three pouches containing powder to be reconstituted in water before oral administration.

In support of this NDA, the Applicant has conducted one phase 1 trial in healthy subjects, one phase 2 trial (Part A in healthy subjects and Part B in patients screening for colonoscopy) and three phase 3 active-controlled trials with the to-be-marketed (TBM) formulation. PLENVU was compared to three different active comparators in three phase 3 trials.

The proposed dosing remigen for PLENVU is either two-day dosing or one-day dosing. In two-day dosing, Dose 1 will be administered in the evening before the colonoscopy and Dose 2 will be administered the morning of the colonoscopy whereas in one-day dosing, both Dose 1 and Dose 2 will be administered in the morning of the colonoscopy approximately 2 hours apart.

PLENVU was submitted under 505(b)(2) regulatory pathway, referencing MOVIPREP® label for its nonclinical findings. MOVIPREP® , marketed by the same Applicant, was approved in 2006 for colon cleansing as a preparation for colonoscopy in adults. MOVIPREP® consists of same osmotic ingredients as the proposed product PLENVU, polyethylene glycol (PEG) 3350, sodium sulfate, sodium ascorbate and ascorbic acid with different amount of each.

Throughout this review, PLENVU will also be refered its code name NER1006 that was used throughout the development program.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed NDA 209381. This NDA is acceptable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness:	Pivotal: Two pivotal phase 3 studies comparing Plenvu with already marketed bowel cleansing products, MOVIPREP® and SUPREP, provides the primary evidence of effectiveness of PLENVU. Plenvu was non-inferior to SUPREP and MOVIPREP® for overall bowel cleansing using Harefield Cleansing Scale (HCS), when administered either as a 2-day overnight split dosing regimen or as a 1-day split dosing regimen on the morning of colonoscopy. Supportive: Dose- or exposure-response analyses were not performed to support effectiveness of PLENVU. One phase 1 study (OUT) was conducted to identify a preferred evening and morning formulation combination based on stool weight. A further Phase II study (OPT) was conducted to assess different taste/flavor, dose volume and dosing sequence to optimize the selected formulation from the phase 1 study to improve patient acceptability and tolerability of proposed product. From the phase 2 study, based on stool weight and cleansing success rate according to the Harefield Cleansing Scale, the OPT007 regimen was selected as the optimal regimen to be further evaluated in phase 3 studies.
General dosing instructions:	The proposed dosing regimens are supported by phase 3 trials. Two-day and One-day dosing regimens: • Two-Day: Dose 1 the evening before the colonoscopy (approx. 4pm to 8pm) and Dose 2 the next morning, approx. 12 hours after the start of Dose 1. • One-Day: Dose 1 the morning of the colonoscopy (approx. 3am to 7am) and Dose 2 approx. 2 hours after the start of Dose 1. • Additional clear fluids must be consumed after each dose of PLENVU® in both dosing regimens Doses: • Dose 1: 100 g of PEG 3350; 9 g of sodium sulfate; 2 g of NaCI; and 1 g of KCI. • Dose 2: o Pouch A: 40 g of PEG 3350; 3.2 g of NaCI; and 1.2 g of KCI o Pouch B: 48.11 g of sodium ascorbate; and 7.54 g of ascorbic acid
Dosing in patient subgroups (intrinsic and extrinsic factors):	No dose adjustment in any patient subgroups based on intrinsic or extrinsic factors is recommended. However, based on the mechanism of action, the following are recommended: • Do not take oral medications within 1 hour of starting each dose of PLENVU • Do not take other laxatives while taking PLENVU. • Use caution when using PLENVU in patients with renal impairment or patients taking concomitant medications that affect renal function (such as diuretics, ACE inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs).

1.2 Post-Marketing Requirements and Commitments

Following post-marketing study is recommended and communicated to the Applicant.

3371-4: A phase 1 pharmacokinetic study to adequately characterize the PK of PEG 3350 and its metabolites, triethylene glycol (TEG), diethylene glycol (DEG), and ethylene glycol (EG), and its secondary metabolites such as glycolic acid (GA), diglycolic acid (DGA), Oxalic acid (OA) and hydroxyethoxyacetic Acid (HEAA) in healthy subjects. Adequate bioanalytical assay methods with acceptable sensitivity should be developed for all analytes.

Rationale:

PEG 3350, polyethylene glycol 3350, is one of the active ingredients of Plenvu, and could potentially be metabolized to multiple metabolites in vivo, if absorbed. There has been a notion that PEG3350 would not be absorbable upon oral administration because of its high molecular weight, and thus, the systemic exposure to PEG3350 and its metabolites have not been historically well characterized despite its wide spread use (e.g., colon preparation agencies). Importantly, some metabolites of PEG, such as ethylene glycol, and diethylene glycol, have been linked to potential toxicities in published literatures. Per published literature, PEG metabolites of interest are triethylene glycol, diethylene glycol, ethylene glycol, glycolic acid, diglycolic acid, glyoxylic acid, glycoaldehyde, oxalic acid, and 2-hydroxyethoxyacetic acid (HEAA).

In this NDA, PEG 3350 concentrations found to be measurable in plasma when evaluated for a prototype formulation. However, PEG3350 concentration in plasma was not measured for the to-be-marketed formulation. Additionally, the systemic exposures of PEG metabolites after Plenvu administration were not studied and are unknown at this point. During the pre-NDA meeting dated 02/02/2016, the FDA had requested the sponsor to measure the PK of PEG3350 related metabolites. The sponsor clarified that blood samples from the clinical trial were no longer available for additional analyses for metabolites of PEG, and proposed to conduct a post-marketing study. The FDA agreed that the PK evaluation of PEG3350-related metabolites in human could be conducted as a post-marketing study. As such in this study, the systemic exposure of PEG3350 and its metabolites will be characterized for the to-be-marketed Plenvu. This study results should be used to inform the PK assessment for PEG and PEG metabolites in pediatric patients.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Pharmacology

In the PLENVU, PEG3350, sodium sulfate, sodium ascorbate and ascorbic acid are the principle osmotic laxative active ingredients while sodium chloride and potassium chloride are included to maintain the electrolyte balance. The primary mode of action is osmotic action of the components of PLENVU which induce the laxative effect to produces a copious watery diarrhea.

Clinical Pharmacokinetics

The PK of PLEVU was not characterized with phase 3/TBM formulation. PK was assessed in the phase 1 study, OUT. Below is the the summary PK of PEG3350, ascorbate, and sulfate following an interim regimen (E3/M3) in the phase 1 study, OUT, as it has the most similar composition to the Phase3/TBM

formulation among the regimens that had PK evaluation in OUT study. Please refer to section 3.3.5 for formulation difference between Phase 3/TBM formulation and E3/M3 regimen.

Table 1: Mean (SD) Plasma Pharmacokinetic Data Following Two-Day Split-Dosing Regimen of 140 g PEG 3350, 33.9 g Sodium Ascorbate, 9 g Sodium Sulfate, 20.1 g Ascorbic Acid, 2.8 g Sodium Chloride and 1.3 g Potassium Chloride in Healthy Subjects from E3/M3 regimen in Phase 1 OUT study (N=21)

PK Parameter	**PEG 3350**	**Ascorbate[1]**	**Sulfate[1]**
C_{max} [µg/mL]	2.7 (1.17)	70.8 (22.37)	17.6 (4.80)
t_{max} [h]	3.0 (0.61)	16.8 (0.75)	8.1 (5.51)
AUC(0-t_{last})[2] [(µg/mL)*h]	17.3 (7.19)	433.1 (157.29)	206.2 (74.32)
V_d [l]	48,481 (29,811)	1,026 (675)	231 (205)
$t_{1/2}$ [h]	4.1 (2.34)	7.2 (6.16)	10.5 (15.19)

SD = standard deviation; C_{max} = maximum concentration; t_{max} = time to maximum concentration from start of dosing; AUC(0-t_{last}) = area under the curve from t_0 to t_{last}; V_d = volume of distribution; $t_{1/2}$ = half-life. . E = evening dose M = morning dose

1 Baseline-corrected

2 PK samples were collected up to 7 hours post-evening dose and 56 hours post morning dose where evening dose and morning doses were administered approximately 14 hours apart

Following oral administration, about 85% to 99% of a 140 g oral PEG 3350 dose is excreted in fece; up to 69% to 73% of a 9 grams oral sodium sulfate dose is excreted in feces, with approximately 43% recovered in the urine. Approximately 69% of a 50 grams oral ascorbate dose is excreted in feces and up to 5% of the 50 grams oral ascorbate dose is recovered in the urine.

The baseline plamsa ascorbic acid concentration was approximately 12 ug/mL and baseline uncorrected mean Cmax for ascorbic acid was 81.18 (223.52: SD) ug/mL. Plasma ascorbic acid was return to its baseline level approximately 36 hours after the evening dose or 22 hours after the morning dose of the interim formulation (E/M3).

The baseline plamsa sulfate level was approximately 30 ug/mL and baseline uncorrected sulfate mean Cmax was 48.05 (6.01: SD) ug/mL. Plasma sulfate level returns to its baseline level approximately 20 hour after the evening dose or 6 hours after the morning dose for the interim formulation (E/M3).

Excretion of oxalic acid in urine and feces were relatively delayed and prolonged (Day 2 through Day 4 in urine and Day 3 to Day 4 in feces) compared to that of ascorbic acid (majority excreted on Day 2 in both urine and feces) or PEG 3350 (majority excreted on Day 1 to Day 2 in feces) reflecting the slow formation of oxalic acid despite unmreaurable plasma concnetration.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is as follows:

- Two-Day: Dose 1 the evening before the colonoscopy (approx. 4 pm to 8 pm) and Dose 2 the next morning (approx. up to 12 hours after the start of Dose 1).

- One-Day: Dose 1 the morning of the colonoscopy (approx. 3 am to 7 am) and Dose 2 a minimum of 2 hours after the start of Dose.

Additional clear fluids must be consumed after each dose of PLENVU® in both dosing regimens

The proposed dose is as follows:

- Dose 1: 100 g of PEG 3350; 9 g of sodium sulfate; 2 g of NaCl; and 1 g of KCl
- Dose 2:
  - Pouch A: 40 g of PEG 3350; 3.2 g of NaCI; and 1.2 g of KCl
  - Pouch B: 48.11 g of sodium ascorbate; and 7.54 g of ascorbic acid

2.2.2 Therapeutic individualization

Extrinsic Factors:

No dose adjustment in any of patient subgroups based on extrinsic factor is recommended. However, based on the mechanism of action, the the applicant proposed the following:

- Do not take oral medications within 1 hour of starting each dose of PLENVU
- Do not take other laxatives while taking PLENVU.

The applicants's proposal regarding DDI is acceptable and consistent with other colon cleansing agents' labeling.

Intrinsic Factors:

No dose adjustment in any patient subgroups based on intrinsic factor is recommended. However, based on the mechanism of action, the applicant proposed the following:

- Use caution (b) (4) in patients with (b) (4) renal impairmen (b) (4) or patients taking concomitant medications that affect renal function (such as diuretics, ACE inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs).

OCP does not believe the phase 3 study contains an adequate number of patients with moderate renal impairment (only aproximately 5%) to make any conclusion about the relative safety in this population. In addition, the Clinical Division (DGIEP) is concerned that even patients with lesser degrees of renal impairment may still be at increased risk compared to patient with normal renal function. Please refer to the clinical review for further detail. Therefore, the Division recommends to use caution in patients with all degrees of renal impairment when using PLENVU.

2.3 Outstanding Issues

A PMR is being issued to meassure the plasma exposure of PEG3350 and its metabolites. Please refer to section 1.2 for further details.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Overview of the Product:

Plenvu powder (NER1006) for oral solution is a new combination of known osmotic laxative drug substance. Plenvu is designed as a split-dosing formulation containing two fixed doses of osmotically-active powders to be reconstituted in water: The first dose contains PEG3350, sodium sulfate, sodium chloride and potassium chloride in a single pouch. The second dose consists of two pouches (Pouch A and Pouch B) that together contain PEG3350, sodium ascorbate, ascorbic acid, sodium chloride and potassium chloride. Each dose is reconstituted to a volume of 16 fl. oz. with water. A single treatment of PLENVU is thus a one liter preparation. In the Plenvu formulation, PEG3350, sodium sulfate, sodium ascorbate and ascorbic acid are included as the principle active ingredients while sodium chloride and potassium chloride are included to maintain the electrolyte balance.

Other colon cleansing agents with simiar composition are available on the US market. MOVIPREP® (arrpoved in 2006), which was used as a comparator in one of the phase 3 studies, also contains PEG3350, sodium ascorbate, ascorbic acid, sodium sulfate, sodium chloride and potassium chloride and also available as slit-dose regimen (2-days) and one day regimen (evening only). Compared to MOVIPREP®, Plenvu contains a lower amount of PEG3350 (140 g in Plenvu vs. 200 g in MOVIPREP) and sodium sulfate (9 g in PLENVU vs. 15 g in MOVIPREP) and a higher amount of ascorbate compoent (48.11 g of sodium ascorbate and 7.54 g ascorbic acid in PLENVU vs. 11.8 g of sodium ascorbate and 9.4 g ascorbic acid in MOVIPREP).

Regulatory Background:

This NDA for PLENVU was initially submitted on 09/16/2016 and it was fileable from clinical pharmacology standpoint. Please see Clinical Pharmacology filling review dated 11/15/2016. However, the Applicant had withdrawn the NDA application on 11/15/2016 due to FDA's substantive comment on the phase 3 clinical trial datasets. Subsequently, this original NDA is resubmitted on 4/13/2017 (SND 11).

During the pre-NDA meeting dated 02/02/2016, the FDA had requested the sponsor to measure the PK of PEG3350 related metabolites ethylene glycol (EG), diethylene glycol (DEG), and glycolic acid. The sponsor clarified that biologic samples from the clinical trial were no longer available for additional analyses. Therefore, the FDA stated that it is acceptable to conduct the PK evaluation of PEG3350-related metabolites in human as a PMR. Please refer to the meeting minutes for the detailed discussion.

3.2 General Pharmacology and Pharmacokinetic Characteristics

PLENVU powder for oral solution is an osmotically-acting laxative that is designed as a split-dosing formulation containing two fixed doses of osmotically-active powder to be reconstituted in water. It can either be taken over 2 days (evening before the colonoscopy and morning of colonospopy) or in 1 day on the morning of the colonoscopy with doses administered 2 hours apart.

The PK of PLEVU was not characterized with the phase 3/TBM formulation. PK was assessed in the phase 1 study, OUT, in groups E3/M3, E3/M1 and MOVIPREP® regimens which have different composition than that of the phase 3/TBM formulation. The phase 2 study, OPT, had limited PK evaluation. Therefore, the PK assessment will focus on the result of the OUT study's E3/M3 regimen, as E3/M3 has the most similar composition to the phase 3/TBM formulation among the regimens evaluated

in the OUT study. Please refer to section 3.3.5 for formulation difference between phase 3/TBM formulation and E3/M3 regimen.

Table 2: Mean (SD) Plasma Pharmacokinetic Data Following Two-Day Split-Dosing Regimen of 140 g PEG 3350, 33.9 g Sodium Ascorbate, 9g Sodium Sulfate, 20.1 g Ascorbic Acid, 2.8 g Sodium Chloride and 1.3 g Potassium Chloride in Healthy Subjects from E3/M3 regimen in Phase 1 OUT study (N=21)

PK Parameter	**PEG 3350**	**Ascorbate[1]**	**Sulfate[1]**
C_{max} [µg/mL]	2.7 (1.17)	70.8 (22.37)	17.6 (4.80)
t_{max} [h]	3.0 (0.61)	16.8 (0.75)	8.1 (5.51)
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$t_{1/2}$ [h]	4.1 (2.34)	7.2 (6.16)	10.5 (15.19)

SD = standard deviation; C_{max} = maximum concentration; t_{max} = time to maximum concentration from start of dosing; AUC(0-t_{last}) = area under the curve from t_0 to t_{last}; V_d = volume of distribution; $t_{1/2}$ = half-life. E = evening dose M = morning dose

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2 PK samples were collected up to 7 hours post-evening dose and 56 hours post morning dose where evening dose and morning doses were administered approximately 14 hours apart

Following oral administration, about 85% to 99% of a 140 g oral PEG 3350 dose is excreted in fece; up to 69% to 73% of a 9 grams oral sodium sulfate dose is excreted in feces, with approximately 43% recovered in the urine; Approximately 69% of a (b) (4) grams oral ascorbate dose is excreted in feces and up to 5% of the (b) (4) grams oral ascorbate dose is recovered in the urine.

The baseline plamsa ascorbic acid concentration was approximately 12 ug/mL and baseline uncorrected ascobbic acid Cmax was 81.18 (223.52 SD) ug/mL. Plasma ascorbic acid was return to its baseline level approcimately 36 hour after after the evening dose or 22 hours after the morning dose of the interim formulation (E/M3).

The baseline plamsa sulfate level was approximately 30 ug/mL and baseline uncorrected sulfate Cmax was 48.05 (6.01 SD) ug/mL. Plasma sulfate level returns to its baseline level approximately 20 hour after the evening dose or 6 hours after the morning dose for the interim formulation (E/M3).

3.3 Clinical Pharmacology Review Questions

The clinical development program for PLEVU (NER1006) consisted of following 5 studies:

- NER1006-01/2011 (OUT): A Phase 1 proof-of-concept study evaluating pharmacokinetic, pharmacodynamics, safety and tolerability conducted in Romania
- NER1006-01/2012 (OPT): A Phase 2 study evaluating pharmacodynamics and clinical evaluation using taste/flavor-optimized doses formulations conducted in Germany.
- Three Phase 3 clinical safety, efficacy and tolerability studies using the final dose formulations conducted in the US and European Union (EU) with randomized, parallel group design including three different active comparator drugs:
    - NER1006-01/2014(NOCT): active comparator: trisulfate bowel cleansing solution (SUPREP®)

- NER1006-02/2014(MORA): active comparator: MOVIPREP®
- NER1006-03/2014(DAYB): active comparator: a solution containing SP+MS (CITRAFLEET®)

This NDA submission does not contain any in-vitro drug-drug interaction or metabolism studies.

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The applicant had conducted three phase 3 studies comparing Plenvu with already marketed bowel cleansing products, MOVIPREP®, SUPREP®, and CITRAFLEET® to support the primary evidence of efficacy and safety of PLENVU. As CITRAFLEET® is not an approved product in the US, the results of phase 3 study NER1006-03/2014(DAYB), which uses CITRAFLEET as the comparator, will not be discussed here. In the all phase 3 studies, the applicant used Harefield Cleansing Scale (HCS) to measure the cleansing efficacy of bowel preparation.

Harefield Cleansing Scale (HCS) measures the quality of cleansing given a score of 0–4 (inclusive) for the five segments: ascending colon and cecum, transverse colon, descending colon, sigmoid colon, and rectum, as follows.

Description of Colonic Cleansing Assessment using Harefield Cleansing Scale

Segment Score	**Description**
0	Irremovable, heavy, hard stools
1	Semi-solid, only partially removable stools
2	Brown liquid/removable semi-solid stools
3[a]	Clear liquid
4[a]	Empty and clean
Grade	**Description**
A	All five segments scored 3 or 4
B	One or more segments scored 2, other segments scored 3 or 4
C	One or more segments scored 1, other segments scored 2, 3 or 4
D	One or more segments scored 0

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

a. For the purpose of the Phase III clinical studies, for rating cleansing success in the colon ascendens, a score of 3 was defined as "Good" and a score of 4 was defined as "Excellent."

The phase 3 studies had also evaluated two different Plenvu dosing regimens, two-day, split dosing regimen and one-day morning dosing regimen compared to reference products.

- Two-Day Split-Dosing Regimen: Allows for an overnight gap between two doses. Dose 1 is taken in the evening before the clinical procedure [approximately 6 pm] and Dose 2 is taken the next morning, on the day of the colonoscopy, approximately 12 hours after the start of Dose 1. Note: Dose 1 can be up to 2 hours earlier or later than 6 pm.
- One-Day Morning Dosing Regime: Gives both doses in the morning of the day of colonoscopy. Dose 1 is taken at approximately 5 am and Dose 2 is taken approximately 2 hours after the start of Dose 1. Note: Dose 1 can be up to 2 hours earlier or later than 5 am.

Plenvu was non-inferior to approved SUPREP and MOVIPREP® for overall bowel cleansing using HCS when administered either as a 2-day overnight split dosing regimen or as a 1-day split dosing regimen on the morning of colonoscopy.

Table 3: Efficacy result (Harefield Cleansing Scale) of Phase 3 studies (NOCT and MORA Studies)

Parameter	NOCT		MORA		
	NER1006 (N=276)	Trisulfate (N=280)	NER1006 2-Day (N=275)	NER1006 1-Day (N=275)	MOVIPREP® (N=272)
Primary Endpoint 1: Overall Bowel Cleansing Quality					
HCS Success[a], n (%)	235 (85.1)	238 (85.0)	253 (92.0)	245 (89.1)	238 (87.5)
Primary Endpoint 2: Cleansing Rate in the Colon Ascendens					
HCS Excellent plus Good[b], n (%)	99 (35.9)	82 (29.3)	87 (31.6)	93 (33.8)	41 (15.1)

Source: Module 2.7.3, Table 2.7.3.3-5.
HCS = Harefield Cleansing Scale; N = total number of patients; n = number of patients with data.
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.

Dose- or exposure-response analyses were not performed to support effectiveness of PLENVU.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimens appear to be reasonable for the general targeted patient population. The preferred evening and morning formulation combination was identified in the phase 1 OUT study based on assessment of stool weight (PD), which is considered a surrogate measure for bowel cleansing efficacy. Based on the stool weight result of the OUT study, formulation E3 and M1 were identified as the optimal evening and morning formulations. The OPT study was conducted to assess different taste/flavor, dose volume and dosing sequence to optimize the selected formulation of the E3 and M1 to improve the patient acceptability and tolerability of proposed product. In the phase 2 study, the OPT007 group was selected as the optimal regimen to be further evaluated in Phase 3 studies based on stool weight and cleansing success rate according to the Harefield Cleansing Scale©. Although OPT007 group has the same amount and same sequence of active ingredients as the phase3/TBM formulation, OPT007 group was further optimized in regards to its excipeints to create the phase3/TBM formulation.

Dose Selection Rationale:

Formulation Optimization:

The preferred evening and morning formulation combination was identified in phase 1 NER1006-01/2011 (OUT) study based on the assessment of stool weight, which is considered a surrogate measure for bowel cleansing efficacy.

NER1006-01/2011 (OUT) was an was a randomized, open-label, single-centered phase 1 study in 161 healthy subjects with 2 parts (Part A and part B) to investigate the PD (stool weight) of various modified, low-volume PEG3350 and ascorbic acid bowel cleansing solutions. Subjects were randomized (1:1:1:1)

to 1 of 4 treatment groups in each part of the study. Each subject received the oral solution regimen as a split dose:

- Evening dose: Day 1: start intake between 5 PM and 6PM for an intake period of up to 2 hours after fasting from 2 PM,
- Morning dose: Day 2; start intake between 7 AM and 8AM for an intake period of up to 2 hours. 4 hours after complete intake of the morning dose, the first meal was provided, but not before completion of the planned safety laboratory blood draw,

Investigational drug dosing was combined with additional water intake, 875 mL for modified PEG+ASC formulations and 500 mL for MOVIPREP® after the end of the intake of each dose.

The primary PD variable to select formulation was the stool weight output generated by the investigational drug (combined evening and morning dosing on Day 1 and Day 2) from the start of the intake and the following 24 hours. A stool output of around 3000 g was the preferred goal.

Part A: Three different evening doses (E2, E3 and E-IP) were combined with a fixed morning dose (M3). In addition, 1 group of subjects received MOVIPREP® as the reference product. The E3/M3 group and the MOVIPREP® group had achieved the preset preferred goal of reaching a stool weight of 3000 g. Therefore, evening dose E3 was chosen for further evaluation in Part B.

Table 4: Formulations in Part A of OUT Study

Ingredient [g]	Evening dose in 750 mL			Morning dose M3 in 500 mL	MOVIPREP® Even + Morn. in 2000 mL
	E2	E3	E-IP		
PEG 3350	100	100	75	40	200
Sodium sulfate	6.0	9.0	5.6	-	15.0
Sodium ascorbate	-	-	-	33.9	11.8
Ascorbic acid	-	-	-	20.1	9.4
Sodium chloride	1.6	2.0	2.0	2.8	5.4
Potassium chloride	0.7	1.0	0.8	1.3	2.0
Osmolality of powder dose					
Volume (mL) of water to be added to achieve osmolality of approx. 350 mOsm/kg	915	1080	795	1600	1235 + 1235

Table 5: Part A: Summary statistics for stool weights

Sum of stool weight [g] (Median [Q1; Q3])			
E2/M3 (N = 20)	E3/M3 (N = 21)	E-IP/M3 (N = 20)	MOVIPREP® (Evening and Morning) (N = 20)
2981.30 [2741.55; 3435.55]	3493.20 [2982.40; 3804.30]	2796.80 [2641.00; 3296.25]	3145.95 [2643.95; 3280.65]

Q1 = 1st quartile; Q3 = 3rd quartile E = evening dose, M = morning dose

Part B: The selected evening dose formulation from Part A (E3 formulation) was combined with 4 different morning dose formulations (M1, M5, M5 and M-IP) to assess the impact on stool output. Only the morning dose M1 reached the pre-set goal of reaching a stool weight of 3000 g.

Table 6: Formulations of Morning Doses in Part B of OUT Study

Ingredient [g]	M1 in 500 mL	M4 in 500 mL	M5 in 500 mL	M-IP in 500 mL
PEG 3350	40	40	40	(b) (4)
Sodium sulfate	-	6.0	-	
Sodium ascorbate	56.6	33.9	33.9	
(b) (4)				(b) (4)
Ascorbic acid	-	-	-	
Sodium chloride	3.5	2.8	3.1	
Potassium chloride	2.2	2.0	1.3	
(b) (4)	-	-	-	
Osmolality of powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2000	1700	1700	950

Table 7: Summary statistics for stool weights in Part B (FAS, N = 81)

Sum of stool weight [g] (Median [Q1; Q3])			
E3/M1 (N = 20)	**E3/M4** (N = 20)	**E3/M5** (N = 20)	**E3/M-IP** (N = 20)
3128.90 [2299.05; 3433.15]	2546.00 [1666.70; 3199.20]	2440.10 [1620.55; 3449.30]	2466.85 [2059.70; 2912.35]

Q1 = 1st quartile; Q3 = 3rd quartile E = evening dose, M = morning dose

Conclusion: In Part A, only the E3/M3 and MOVIPREP® groups reached stool weight in excess of 3000 g within 24 hr of start of intake. In Part B, only E3/M1 achieved this same target goal. Based on the PD result of the OUT study, formulation E3 and M1 were identified as the optimal evening and morning formulations.

Taste and Flavor Optimization

To improve the patient acceptability and tolerability of the proposed product, a Phase II NER1006-01/2012(OPT) study was conducted to optimize the taste and flavor of the preferred evening and morning doses from Phase I study (E3/M1). A different flavor was assigned to each of the two doses.

NER1006-01/2012(OPT) was an open-label, randomized, Phase 2 study in 240 subjects with two sequential parts (A and B) to investigate the stool weight (PD) of dose and taste-optimised low volume PEG-based bowel cleansing solutions. There were four treatment arms in each part of the study, to which subjects were randomized in a 1:1:1:1 ratio, separately for each part.

- Evening dose: Day 1: start intake between 5 PM and 6PM for an intake period of up to 2 hours after fasting from 2 PM
- Morning dose: Day 2; start intake between 7 AM and 8AM for an intake period of up to 2 hours. 4 hours after complete intake of the morning dose, the first meal was provided, but not before completion of the planned safety laboratory blood draw

Part A, Primary variable:

- Stool weight output generated from the start of investigational drug intake on the evening of Day 1 and the following 24 hours (the desired stool weight target for the study was 2750 g).

Part B, Co-primary variables:

- Stool weight output generated from the start of investigational drug intake on the evening of Day 1 and the following 24 hours (the desired stool weight target for the study was 2750 g).
- Cleansing success rate (according to the Harefield Cleansing Scale©).

Table 8: NER1006 Formulations in OPT Study:

Ingredient [g]	TF048 (in 750 mL) ≅ E3	TF047 (in 500 mL) "Reduced reconstitution volume" version of TF048	TF043 (in 500 mL) ≅ M1	TF044 (in 500 mL) "Low ascorbate" version of TF043
PEG 3350	100	100	(b) (4)	
Sodium sulfate	9.0	9.0		
Sodium ascorbate	-	-		
Ascorbic acid	-	-		
Sodium chloride	2.0	2.0		
Potassium chloride	1.0	1.0		
Osmolality of powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	1100	1125	1850	1500

Part A investigated the effect of different sequences of dosing and dose volumes in healthy subjects. Stool outputs in all regimens in Part A were greater than 2750 g and greater than that of MOVIPREP®, but only those for OPT002 and OPT003 were statistically significant (p-value was <0.1). In addition, OPT003 had the highest stool weight compared to all other regimens. Based on the stool output, OPT003 was selected for further evaluation in Part B.

Table 9: NER1006 and MOVIPREP® (OPT004) Regimens Used in OPT Study

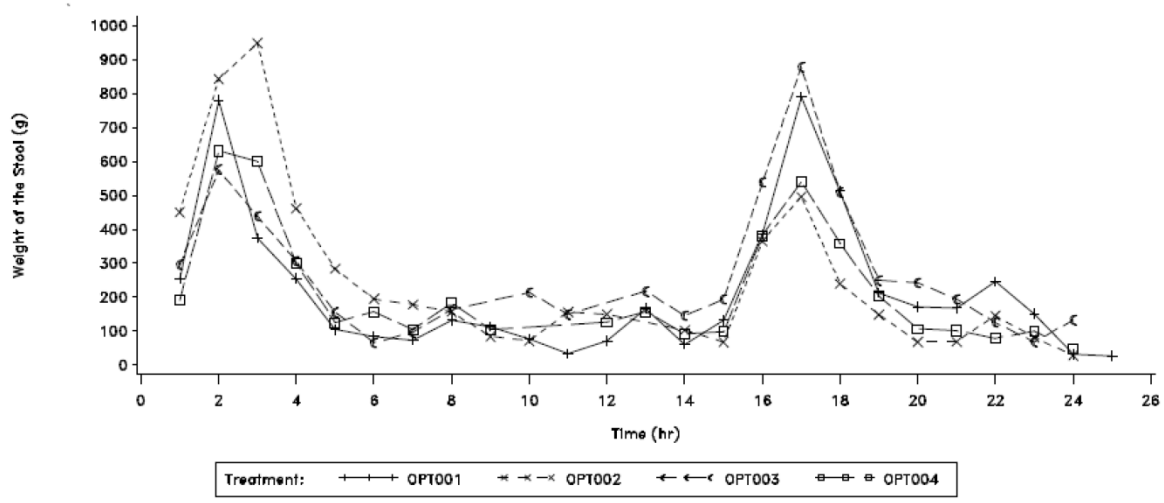
Interval	Part A			
	OPT001	**OPT002**	**OPT003**	**OPT004**
Evening	TF048 (in 750 mL)	TF043 (in 500 mL)	TF047 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+1000 mL	+500 mL
Morning	TF043 (in 500 mL)	TF048 (in 750 mL)	TF043 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+1000 mL	+500 mL
Total intake volume	3000 mL	3000 mL	3000 mL	3000 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2950	2950	2975	2470

Table 10: Summary Statistics for Stool Weights (OPT Study)

Statistic	Part A			
	OPT001 (N=30)	OPT002 (N=29)	OPT003 (N=30)	MOVIPREP® (N=30)[a]
Mean (SD) [g]	2951.0 (873.77)	3218.7 (809.89)	3399.3 (575.78)	2490.8 (879.24)
Median (range) [g]	2978.75 (729.2 - 4328.5)	3326.20 (912.0 - 4559.1)	3513.00 (2114.5 - 4216.9)	2597.40 (375.8 - 4505.0)
[90% CI]	[2679.99;3222.10]	[2962.85;3474.52]	[3220.65;3577.88]	[2213.02;2768.51
p-value[b]	0.2176	0.0042	<0.0001	0.8764

a: n = 29; b = one-sample t-test

Figure 1: Mean Stool Weight Over Time Part A



In part A, it appears that first bowel movement occurred about 1-2 hours after the evening dose and maximum stool outpout occurred between 1-6 hours post evening and morning doses where evening and morning doses were administered about 14 hours apart.

Part B took the optimal dose sequence and volume from Part A (OPT003), and compared it to a lower ascorbate preparation and a different total intake volume of the preparation (OPT006, OPT007) in colorectal cancer screening population. Both OPT003 and OPT007 regimen resulted in target stool weight of greater than 2750 g in Part B, while OPT007 had higher stool weight compared to OPT003 (3215.1 g in OPT007 vs. 3050.5 g in OPT003). In addition, OPT003 and OPT007 also had 100% cleansing success rate based on the Harefield Cleansing Scale. Based on the stool output and cleansing success rate, OPT007 group was selected for further clinical testing in phase 3 studies.

Table 11: NER1006 and MOVIPREP® (OPT004) Regimens Used in OPT Study

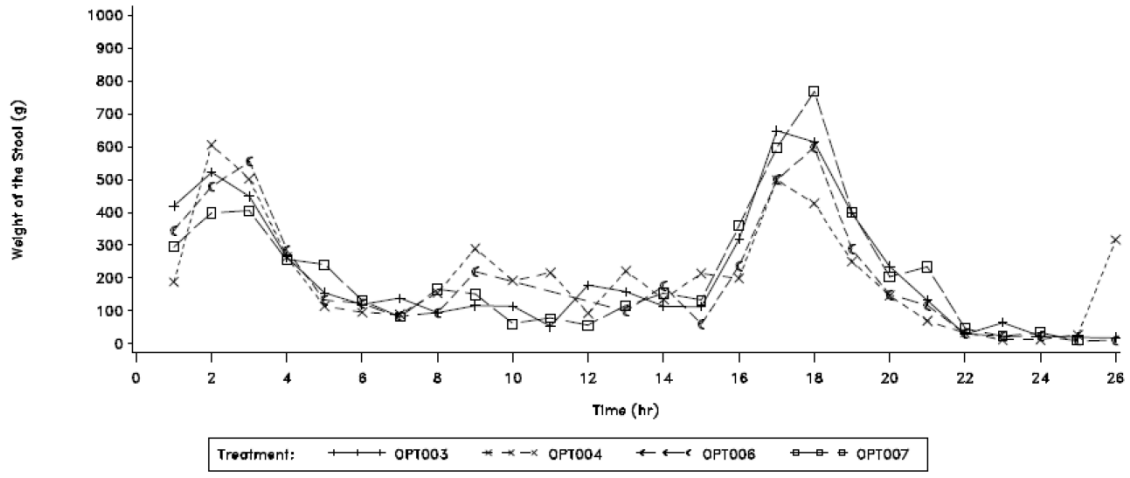
	Part B			
	OPT003	**OPT007**	**OPT006**	**OPT004**
Evening	TF047 (in 500 mL)	TF047 (in 500 mL)	TF047 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+1000 mL	+500 mL	+1000 mL	+500 mL
Morning	TF043 (in 500 mL)	TF043 (in 500 mL)	TF044 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+1000 mL	+500 mL	+1000 mL	+500 mL
Total intake volume	3000 mL	2000 mL	3000 mL	3000 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2975	2975	2625	2470

Table 12: Summary Statistics for Stool Weights (OPT Study)

	Part B			
	OPT003 (N=30)	**OPT007 (N=30)**	**OPT006 (N=30)**	**MOVIPREP® (N=30)**
Mean (SD) [g]	3050.5 (705.41)	3215.1 (634.25)	2675.3 (612.15)	2487.1 (634.69)
Median (range) [g]	3065.70 (1357.9 - 4102.0)	3290.20 (1501.7 - 4433.3)	2657.95 (1153.8 - 3846.8)	2636.40 (968.9 - 3430.8)
[90% CI]	[2831.62;3269.28]	[3018.32;3411.84]	[2485.41;2865.21]	[2290.25;2684.03]
p-value[b]	0.0268	0.0004	0.4907	0.9691

a: n = 29; b = one-sample t-test

Figure 2: Mean Stool Weight Over Time Part B



Similar to part A, it appears that first bowel movement occurred about 1-2 hours after the evening dose and maximum stool outpout occurred between 1-6 hours post evening and morning doses where evening and morning doses were administered about 14 hours apart.

Table 13: Phase II NER1006-01/2012(OPT) Study Results - Stool Output and Cleansing Success

Formulation*	Cleansing Success (HCS grade A+B) n (%)	HCS Grade A n (%)	HCS Grade B n (%)	HCS Grade C n (%)	HCS Grade D n (%)
OPT007	30 (100)	28(93.33)	2 (6.67)	0(0.00)	0 (0.00)
OPT003	30(100)	22 (73.33)	8 (26.67)	0(0.00)	0 (0.00)
OPT006	27(90)	20 (66.67)	7 (23.33)	3 (10.00)	0 (0.00)
OPT004	27(90)	6 (20.00)	21 (70.00)	2 (6.67)	1 (3.33)

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

There is not alternative dosing regimen for subpopulations based on intrinsic factors. The Applicant proposed to use caution when using PLENVU in patients with severe renal impairment based on the mechanism of action and population studied in phase 3 trials. As the phase 3 studies did not include adequate number of patients with moderate renal impairment, FDA recommend to use caution when using PLENVU in patients with all degree of renal impairment. The FDA's recommended labeling language regarding renal impairment is consistent with the current labeling for other colonoscopy products.

The applicant did not conduct any dedicated renal or hepatic impairment study to assess the effect of intrinsic factors in this NDA submission. According to the applicant, in the PLENVU clinical studies, patients with renal impairment were permitted, with approximately 68% of patients having mild or moderate renal impairment. However, the use of PLENVU in patients with severe renal impairment has not been evaluated. Based on the mechanism of action and design of the Plenvu clinical studies, the sponsor proposed "use PLENVU with caution in patients with (b) (4) renal impairment (b) (4) or patients taking concomitant medications that affect renal function (such as diuretics, ACE inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs)'. However, after reviewing the phase 3 data, it was noted that in two phase 3 studies, while 60-65% patient had mild renal impariemnt, only 5% patient had moderate renal impariement. Therefore, OCP does not believe the phase 3 study contains adequate number of patient with moderate renal impairment to make any conclusion about the relative safety in this population. In addition, the Clinical Division (DGIEP) is concerned that even patients with lesser degrees of renal impairment may still be at increased risk compared to patient with normal renal function. Please refer to the clinical review. Therefore, FDA recommends to use caution in patients with all degree of renal impairment when using PLENVU..

> Internal Note: Moviprep, Colyte, Golytely, halflytely, Nulytely, Suclear labels recommend to use caution in patient with imparired renal function, without any specification to certain degree of renal impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The applicant proposed to administer oral medications at least 1 hour before the start of administration of each dose of PLENVU and not to use PLENVU with other stimulant laxative concomitantly based on the mechanism of action. The applicant 's proposal appears to be reasonable.

DDI:

The applicant did not conduct any *in-vitro or in-vivo* drug-durg interaction studies. As PLENVU is proposed to have a single use for colon cleansing before colonoscopy, the lack of *in-vitro* or *in-vivo* drug-drug interaction studies is acceptable.

Based on the mechanism of action, PLENVU can reduce the absorption of other coadministered drugs. Therefore, the applicant proposed to administer oral medications at least 1 hour before the start of administration of each dose of PLENVU. Based on the stool output data from the phase 2 study, the first bowel movement may occurre about 1-2 hours after the administration of Plenvu (Figure 1 and Figure2). Therefore, tThe applicant 's proposal appears to be reasonable and consistent with other colon cleansing agents' labelings.

Additionally, based on the mechanism of action, the concurrent use of PLENVU with other stimulant laxatives may increase the risk of mucosal ulceration or ischemic colitis. Therefore, the applicant proposed to avoid use of stimulant laxatives (e.g., bisacodyl, sodium picosulfate) while taking PLENVU. The applicant 's proposal appears to be reasonable and consistent with other colon cleansing agents' labelings.

Internal Note: Movie prep, Colyte, hafelytely and Suprep have 1 hr DDI restriction, but does not have laxative DDI

Golytely, nulytely, Suclear has btoh 1 hr DDI restriction and lacative DDI.

Food:

The applicant did not conduct andy food effect study. There is no anticipated food effect, as the intake of food is restricted according to the administration procedure due to the nature of the purpose of the product. The applicant's proposed language regarding food intake is acceptable and consistent with the design of the phase 3 studies,

The applicant's current proposed label:

Do not eat or drink alcohol, milk, anything colored red or purple (b) (4) any other foods containing pulp material.

Two-Day Split-Dosing Regimen

The day before the clinical procedure, (b) (4) they can consume a light breakfast followed by a light lunch which must be completed at least 3 hours prior to the start of the first PLENVU dose.

One-Day Morning Dosing Regimen

The day before the clinical procedure, [redacted] a light breakfast followed by a light lunch, and clear soup and/or plain yogurt for dinner, which should be completed by approximately 8 pm.

The drug administration in relation to food in phase 3 studies were consistent with the proposed labeling.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

As there was no change from the Phase 3 formulation to the TBM formulation and the propose product PLENVU is an oral solution, no bioequivalence study was conducted.

Table 14: Composition of Phase 3 and TBM NER1006 formulations

Name of Ingredients	Quantity (g/pouch)			Function	Reference
	Dose 1	Dose 2			
	TF067	TF079a (Pouch A)	TF079b (Pouch B)		
Active					
Polyethylene Glycol (PEG) 3350	100.00	40.00	Not present	[redacted]	NF
Sodium Sulfate	9.00	Not present	Not present		USP
Sodium Chloride	2.00	3.20	Not present		USP/NF
Potassium Chloride	1.00	1.20	Not present		USP/NF
Sodium Ascorbate	Not present	Not present	48.11		USP/NF
Ascorbic Acid	Not present	Not present	7.54		USP/NF
Excipient					
Sucralose	[redacted]	Not present	Not present	[redacted]	NF
Aspartame	Not present	[redacted]	Not present		NF
Encapsulated Citric Acid	[redacted]	Not present	Not present		In-house
Mango Flavor # [redacted]		Not present	Not present	Flavoring	In-house
Fruit Punch Flavor # [redacted]	Not present	[redacted]	Not present		

However, the formulations used in the Phase 1 OUT study and Phase 2 OPT study were slightly different from phase3/TBM formulation.

Table 15: NER1006 Dose 1 Formulations used in OUT Study

Ingredient	Function	E2 (g in 750 mL)	E3 (g in 750 mL)	E-IP (g in 750 mL)
Polyethylene glycol 3350	(b) (4)	100	100	75
Sodium sulfate (b) (4)		6	9	5.6
Sodium chloride		1.6	2.0	2.0
Potassium chloride		0.7	1.0	0.8
Aspartame		0.118	0.118	0.118
				(b) (4)

Table 16: NER1006 Dose 2 Formulations used in OUT Study

Ingredient	Function	M1 (g in 500 mL)	M3 (g in 500 mL)	M4 (g in 500 mL)	M5 (g in 500 mL)	MIPa-1 (g in 500 mL)	MIPa-2 (g in 500 mL)
Pouch A							
Polyethylene glycol 3350	(b) (4)						(b) (4)
Sodium sulfate (b) (4)							
Sodium chloride							
Potassium chloride							
Aspartame (b) (4)							
Pouch B							
Ascorbic acid	(b) (4)						(b) (4)
Sodium ascorbate (b) (4)							

Based on the clinical results (stool weight) of the OUT study, formulations E3 and M1 were identified as the optimal evening and morning formulation to be further evaluated in phase 2 study.

Table 17: NER1006 Formulations used in Phase II OPT Study

Ingredient	Function	TF043 (g)	TF044 (g)	TF047 (g)	TF048 (g)
Pouch A					
Polyethylene glycol 3350	(b) (4)	40.00	40.00	(b) (4)	
Sodium sulfate			(b) (4)		
(b) (4)					
Sodium chloride					
Potassium chloride					
Aspartame					
Sucralose					
Fruit Punch flavor					
(b) (4)					
Pouch B					
Ascorbic acid	(b) (4)	7.54	(b) (4)		
Sodium ascorbate		48.11			

Table 18: Clinical Regimens for NER1006 in OPT Study

Investigational Product Code Number	Evening Dose		Morning Dose		Total Volume of Administered Preparation (including Additional Clear Fluid)
	Formulation Number	Volume for Reconstitution (mL)	Formulation Number	Volume for Reconstitution (mL)	
OPT001	TF048	750	TF043	500	3 liters
OPT002	TF043	500	TF048	750	3 liters
OPT003	TF047	500	TF043	500	3 liters
OPT004	MOVIPREP®	1000	MOVIPREP®	1000	3 liters
OPT006	TF047	500	TF044	500	3 liters
OPT007	TF047	500	TF043	500	2 liters

Clinical regimen OPT007 was identified as the optimal regimen based on stool weight and cleansing efficacy to be further examined in phase 3 studies. Although OPT007 regimen has the same amount and same sequence of of active ingredients as the phase 3/TBM formulation. OPT007 group was further optimized in regards to its excipeints to achive the phase 3/TBM formulation.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

• Which metabolites have been selected for analysis and why?

PEG3350 was measured in plasma and feces but was not measured in urine. Sulfphate, ascorbic acid and its metabolite oxalic acid were measured in plasma, urine and feces.

Metabolites of PEG 3350 were not analyzed in both Phase 1 OUT study and Phase 2 OPT study . However, it was agreed upon during the pre-NDA meeting that the sponsor would conduct a study to evaluated the metabolites of PEG3350 as PMC/PMR .

• What bioanalytical methods are used to assess concentrations of the measured moieties?

Analyte	Matrix	Study #	Vendor	Bioanalytical Method	Validation Report #
PEG3350	Plasma	OUT Study	(b) (4)	Protein precipitation followed by LC-MS/MS	(b) (4) 5304
	Urine	None			
	Feces	OUT & OPT study		Liquid extraction followed by LC-MS/MS	8250569 & (b) (4)-11-066-V6
Sulphate	Plasma	OUT Study		Protein precipitation followed by Ion Chromatography with suppresed conductivity detection	8259-871
	Urine	OUT study		Dilution followed by Ion Chromatography with Suppresed conductivity detection	8259-872
	Feces	OUT study		Dilution followed by Ion Chromatography with conductivity detection	(b) (4) 5290
Ascorbic	Plasma	OUT & OPT study		Protein precipitation followed by LC-MS/MS	8256993
	Urine	OUT & OPT study		Dilution followed by LC-MS/MS	8256994
	Feces	OUT & OPT study		Dilution followed by LC-MS/MS	8256995
Oxalic Acid	Plasma	OUT & OPT study		Protein precipitation followed by LC-MS/MS	8256993
	Urine	OUT & OPT study		Dilution followed by LC-MS/MS	8256994
	Feces	OUT & OPT study		Dilution followed by LC-MS/MS	8256995

o What is the concentration range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Analyte	Matrix	Standard Curve Range	Curve fitting techniques	LLOQ
PEG3350	Plasma	0.25-5.0 ug/mL	A linear regression with a 1/concentration^2 weighting	0.25 µg/mL
	Feces	2 to 300 mg/g	Quadratic regression with a 1/concentration^2 weighting	1 mg/g
Sulphate	Plasma	20 to 500 µg/mL	Linear regression with a 1/concentration weighting	20 µg/mL
	Urine	200 to 5000 µg/mL	Linear regression with a 1/concentration weighting	200 µg/mL
	Feces	100 to 10000 ug/g	A linear regression with a 1/concentration^2 weighting	100 µg/mL
Ascorbic	Plasma	1 to 500 µg/mL	Quadratic regression with a 1/concentration^2 weighting	1 µg/mL
	Urine	10 to 5000 µg/mL	Quadratic regression with a 1/concentration^2 weighting	10 µg/mL
	Feces	40 to 20000 µg/g	Quadratic regression with a 1/concentration^2 weighting	40 µg/g
Oxalic Acid	Plasma	10 to 5000 µg/mL	Quadratic regression with a 1/concentration^2 weighting	10 µg/mL
	Urine	10 to 5000 µg/mL	Quadratic regression with a 1/concentration^2 weighting	10 µg/mL
	Feces	100 to 50000 µg/g	Quadratic regression with a 1/concentration^2 weighting	1000 µg/g

o What are the accuracy, precision, and selectivity at these limits?

Analyte	Matrix	Intra-Assay		Inter-Assay	
		Precision (CV%)	Accuracy	Precision (CV%)	Accuracy
PEG3350	Plasma			<13.2%	-4.5% 14.2%
	Feces	<3.9%	-8.0% to 11%	<6.3%	-6.7% to 4%
Sulphate	Plasma	<4.9%	-11% to 3%	<4.05%	-7.33% to 1.73%
	Urine	<6.4%	-6% to 1%	<5.1%	-3% to -1%
	Feces			<4.5%	-15.7% to 8.4%
Ascorbic	Plasma	<13.2%	-13.7% to 7%	<12.3%	-2.5% to -1.0%
	Urine	<8.9%	-5.5% to 5.0%	<8.0%	-6.6% to 3.0%
	Feces	<7.7%	-6.7 % to 7.5%	<7.4%	-3.2% to 3.8%
Oxalic Acid	Plasma	<14%	-13.5% to 4%	<9.4%	-5.5% to -2.5%
	Urine	<11.2%	3.7% to 11%	<8.9%	-2.5% to 9%
	Feces	<13%	-1.1% to 12%	<13.7%	2% to 18%

o What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

All samples were analyzed within the time period for which the long-term stability has been established.

Analyte	Matrix	Freeze-thaw cycle	Benchtop room temp	Processed Sample (autosampler)		Long Term Stability		Stock solution	
				Room Temp	4°C	-20°C	-70°C	Room temp	Fridge
PEG3350	Plasma	4	24 hr		48 hr	12 month		1 month	
	Feces	4			4 days	450 days	450 days	28 days	
Sulphate	Plasma	4	24 hr	7 days		469 days		30 days	
	Urine	4	24 hr	7 days		491 days		15 days	
	Feces	4	24 hr	48 hr		12 month		1 month	
Ascorbic	Plasma	4	24 hr		146 hr	31 days	472 days	6 hr	28 days
	Urine	6	24 hr		99 hr	443 days	443 days		
	Feces	6	18 hr		95 hr	37 days	423 days		
Oxalic Acid	Plasma	4	24 hr		141 hr	472 days	472 days	6 hr	28 days
	Urine	6	24 hr		102 hr	443 days	443 days		
	Feces	6	18 hr		97 hr	423 days	423 days		

4.2 Individual Study Review

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

Title: **Pharmacodynamic evaluation of stool output following oral administration of various low volume PEG3350-based gut cleansing solutions using the split dose intake in healthy subjects**

Sponsor: Norgine Ltd.
Clinical Site: Pierrel Research HP-RO SRL, Albinelor 114A, 300244 Timisoara, Romania
Study Date: 06/01/2011through 09/16/2011

Bioanalytical Site: (b) (4)

OBJECTIVE:

- Investigate the effects of various modified low volume polyethylene glycol (PEG) 3350 and ascorbic acid/ascorbate (PEG+ASC)-based gut cleansing solutions on stool output after split dose intake in healthy subjects with the goal to identify an optimized combination for further clinical testing.
- Characterize the PK profile of key ingredients of the modified PEG+ASC gut cleansing solutions.
- Assess and compare the safety and tolerance of the modified PEG+ASC formulations following oral administration with the MOVIPREP® profile following split dose intake in healthy subjects.

STUDY DESIGN:

This was a phase 1, randomized, open-label, single-center study in 161 healthy subjects with 2 parts (Part A and part B) to investigate the pharmacodynamic effects (stool weight) of various modified low volume PEG+ASC gut cleansing solutions. Subjects were randomized (1:1:1:1) to 1 of 4 treatment group in each part of the study. Each subject received his/her solution regimen as a split dose intake:

- Evening dose: Day 1; start intake between 17:00 and 18:00 hrs for an intake period of up to 2 hours after fasting from 14:00,
- Morning dose: Day 2; start intake between 7:00 and 8:00 hrs for an intake period of up to 2 hours. 4 hours after complete intake of the morning dose, the first meal was provided, but not before completion of the planned safety laboratory blood drawing,
- Investigational drug dosing was combined with at least minimal required additional clear liquid intake (water) after the end of the intake of each dose: 875 mL for modified PEG+ASC formulations and 500 mL for MOVIPREP® (established 2 liter PEG+ASC formulation).

Formulation: powder for oral solution to be dissolved in water

Part A: Three different evening doses (E2, E3 and E-IP) were combined with a fixed morning dose (M3). In addition, 1 group of subjects received MOVIPREP®, as the reference product to assess particularly tolerance and safety.

Table 1: Formulations in Part A of OUT Study – Quantities of Osmotically Active Ingredients and Electrolytes

Ingredient [g]	Evening dose in 750 mL			Morning dose M3 in 500 mL	MOVIPREP® Even + Morn. in 2000 mL
	E2	E3	E-IP		
PEG 3350	100	100	75	40	200
Sodium sulfate	6.0	9.0	5.6	-	15.0
Sodium ascorbate	-	-	-	33.9	11.8
Ascorbic acid	-	-	-	20.1	9.4
Sodium chloride	1.6	2.0	2.0	2.8	5.4
Potassium chloride	0.7	1.0	0.8	1.3	2.0
Osmolality of powder dose					
Volume (mL) of water to be added to achieve osmolality of approx. 350 mOsm/kg	915	1080	795	1600	1235 + 1235

PEG = polyethylene glycol.

Part B: The selected evening dose formulation from Part A (E3 formulation) was combined with 4 different morning dose formulations (M1, M5, M5 and M-IP) to assess the impact on stool output.

Table 2: Formulations of Morning Doses in Part B of OUT Study – Quantities of Osmotically Active Ingredients and Electrolytes

Ingredient [g]	M1 in 500 mL	M4 in 500 mL	M5 in 500 mL	M-IP in 500 mL
PEG 3350	40	40	40	(b) (4)
Sodium sulfate	-	6.0	-	
Sodium ascorbate	56.6	33.9	33.9	
			(b) (4)	
Ascorbic acid	-	-	-	
Sodium chloride	3.5	2.8	3.1	
Potassium chloride	2.2	2.0	1.3	
Sodium hydrogen carbonate	-	-	-	
Osmolality of powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2000	1700	1700	950

PEG = polyethylene glycol.

Study Population:

The study included healthy males and non-pregnant, non-lactating females ages between 18-45 with good health. This study had 161 evaluable subjects, 81 subjects in Part A and 80 subjects in Part B.

Pharmacokinetic Measurements:

PK was only evaluated for the E3/M3, the E3/M1 and the MOVIPREP® group.

Plasma:

Day 1 (Evening Dose): 4 hour (±30 min) and 1 hour (±15 min) before planned start of intake of the evening dose; 0 (begin of oral IMP solution intake), 5, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300 and 420 min after the start of intake of the evening dose.

Day 2 (Morning Dose): one hour (±15 min) before planned start of intake of the morning dose; 0, 5, 15, 30, 45 minutes and , 1, 1.5, 2, 2.5, 3, 4, 6, 8, 14, 23, 26, 29, 32, 35, 38, 50 and 56 hour after the start of intake of the morning dose on Day 2.

Urine:
For baseline assessment, each subject provided a urine sample within 4 hours after admission to the unit on Day 1. In addition, the subjects were asked to empty the bladder within 30 minutes prior to the planned evening dosing time and a sample was taken. After the start of dosing until discharge from the unit, all urine samples were collected completely after each micturition until 15:00 hrs on Day 4.

Feces:
Screened healthy subjects provided 1 stool collection after a complete bowel motion in the 7 days before the planned admission to the unit for baseline evaluation. After admission to the unit, all defecated stools were collected after each bowel movement until 15:00 hrs on Day 4. Stool appearance and weight was determined for each collected stool fraction and stool samples were immediately prepared for PK sample aliquots.

Efficacy/PD:
Primary variable: The primary variable was the stool weight output generated by the investigational drug (combined evening and morning dosing on Day 1 and Day 2) from the start of the intake and the following 24 hours. A stool output of around 3000 g was the preferred goal.

Bioanalytical Method:
All samples were analyzed within the validated stability timeframe.

Table 3: Accuracy of Precision of the Bioanalysis:

Analyte	Matrix	Storage Condition	ISR	QC Samples Accuracy and Precision	Back calculated Standard curve
PEG	Plasma	<-18°C	166/2318 (7.2%)	LoQC (0.75 µg/mL): 9.84%; MeQC (2.5 µg/mL): 7.69%; HiQC (4.5 µg/mL): 8.56%: % CV: <8.56% Accuracy: -1.3% to 4.9%	CV% <5.2% Accuracy: -1% to 2%
	feces	-80°C	88/839 (10.5%)	LoQC (3 mg/g): 7.6%; MeQC (27 mg/g): 9.0%; HiQC (240 mg/g): 5.9%: % CV: <9.0% Accuracy: -8.7% to 0.8%	CV% <6.2% Accuracy: -4.5% to 3.0%
Sulphate	Plasma	-20°C	162/2315 (7%)	LoQC (72 µg/mL): 2.7% MeQC (224 µg/mL): 3.5% HiQD (422 µg/mL): 3.8% CV% < 3.8% Accuracy: -13% to -9.2%	CV% < 3.9% Accuracy: -5.2% to 4.3%
	Urine	-20°C	128/1559 (8.2%)	LoQD (808 µg/mL): 2.3%, MeQC (2310 µg/mL): 2.3%, HiQC (4310 µg/mL): 2.2%,	CV% < 3.0 % Accuracy: -1.5% to 1.3%

				CV% < 2.3% Accuracy: -3.9% to -1%	
	Feces				
Ascorbic	Plasma	-80°C	164/1157 (14%)	LoQC (3 µg/mL): 6.5% MeQC (40 µg/mL): 6.4% HiQC (400 µg/mL): 6.4% CV% < 6.4% Accuracy: -7.7% to -1.7%	CV% < 4.2% Accuracy: -2.0% to 1.0%
	Urine	-80°C	128/775 (16%)	LoQC (30 µg/mL): 8.9% MeQC (400 µg/mL): 5.5% HiQC (4000 µg/mL): 4.4% 5000 µg/mL: 3.6% CV% < 8.9% Accuracy: -3.7% to -0.8%	CV% < 5.5% Accuracy: -2.0% to -1.6%
	Feces	-80°C	82/422 (20%)	LoQC (120 µg/g): 7.3% MeQC (1350 µg/g): 6.1% HiQC (16000 µg/g): 11.0% 40000 µg/g: 7.7% CV% < 11% Accuracy: -2.5% to -2.0%	CV% < 5.2% Accuracy: -1.0% to -0.6%
Oxalic Acid	Plasma	-80°C	No ISR[#] as all	LoQC (30 µg/mL): 7.1% MeQC (400 µg/mL): 7.0% HiQC (4000 µg/mL): 6.5% CV% < 7.1% Accuracy: -2.2% to 1.8%	CV% < 4.5% Accuracy: -2.0% to 2.4%
	Urine	-80°C	108/775 (14%)	LoQC (30 µg/mL): 5.7% MeQC (400 µg/mL): 7.3% HiQC (4000 µg/mL): 5.9% 5000 µg/mL: 4.4% CV% < 7.3% Accuracy: -2.0% to -3.5%	CV% < 6.0% Accuracy: -3.0% to 2.0%
	Feces	-80°C	No ISR[#]	LoQC: (300 µg/g): 8.6% MeQC (3500 µg/g): 7.8% HiQC (40000 µg/g): 13.6% 100000 µg/g: 4.5% CV% < 13.6% Accuracy: -6.5% to -7.0%	CV% < 5.8% Accuracy: -3.3% to -2.5%

[#] No ISR[#] as all oxalic acid concentration in plasma and feces were below LLOQ.

Table 4: Stability of Samples

Analyte	Matrix	Storage Condition	Date of Sample Collection	Date of Sample Analysis	Maximum Storage time	Established Long term stability at the Storage Condition
PEG	Plasma	<-18°C	06/01/2011 through 09/16/2011	04/02/2012 to 07/11/2012	406*	12 month at -20°C
	feces	-80°C	06/01/2011 through 09/16/2011	02/13/2012 to 02/25/2012	269	450 days at -20°C & at -80°C

Sulphate	Plasma	-20°C	06/01/2011 through 09/16/2011	06/06/2012 through 8/14/2012	440	469 days at -20°C
	Urine	-20°C	06/01/2011 through 09/16/2011	6/29/2012 to 8/10/2012	436	491 days at -20°C
	Feces					12 month at -20°C
Ascorbic	Plasma	-80°C	06/01/2011 through 09/16/2011	04/03/2012 to 05/28/2012	362	31 days at -20°C 472 days at -80°C
	Urine	-80°C	06/01/2011 through 09/16/2011	4/24/2012 to 06/28/2012	393	443 days at -20°C & at -80°C
	Feces	-80°C	06/01/2011 through 09/16/2011	05/02/2012 to 06/30/2012	395	37 days at -20°C 423 days at -80°C
Oxalic Acid	Plasma	-80°C	06/01/2011 through 09/16/2011	04/03/2012 to 05/28/2012	362	472 days at -20°C & at -80°C
	Urine	-80°C	06/01/2011 through 09/16/2011	4/24/2012 to 06/28/2012	393	443 days at -20°C & at -80°C
	Feces	-80°C	06/01/2011 through 09/16/2011	05/02/2012 to 06/30/2012	395	423 days at -20°C & at -80°C

*This is not necessarily the actual maximum storage time. But rather it is the possible maximum potential storage time from the first day of sample collection to the last day of sample bioanalysis.

RESULTS:

Efficacy (Stool Weight):

Table 5: Part A: Summary statistics for stool weights

Sum of stool weight [g] (Median [Q1; Q3])			
E2/M3 (N = 20)	**E3/M3 (N = 21)**	**E-IP/M3 (N = 20)**	**MOVIPREP® (Evening and Morning) (N = 20)**
2981.30 [2741.55; 3435.55]	3493.20 [2982.40; 3804.30]	2796.80 [2641.00; 3296.25]	3145.95 [2643.95; 3280.65]

Q1 = 1st quartile; Q3 = 3rd quartile E = evening dose, M = morning dose

E3/M3 group and the MOVIPREP® group had achieved the preset preferred goal of reaching a stool weight of 3000 g. Therefore, evening dose E3 was chosen for Part B.

Table 6: Summary statistics for stool weights in Part B

Sum of stool weight [g] (Median [Q1; Q3])			
E3/M1 (N = 20)	**E3/M4** (N = 20)	**E3/M5** (N = 20)	**E3/M-IP** (N = 20)
3128.90 [2299.05; 3433.15]	2546.00 [1666.70; 3199.20]	2440.10 [1620.55; 3449.30]	2466.85 [2059.70; 2912.35]

Q1 = 1st quartile; Q3 = 3rd quartile E = evening dose, M = morning dose

Only morning dose of M1 reached the pre-set goal of reaching a stool weight of 3000 g.

PK:

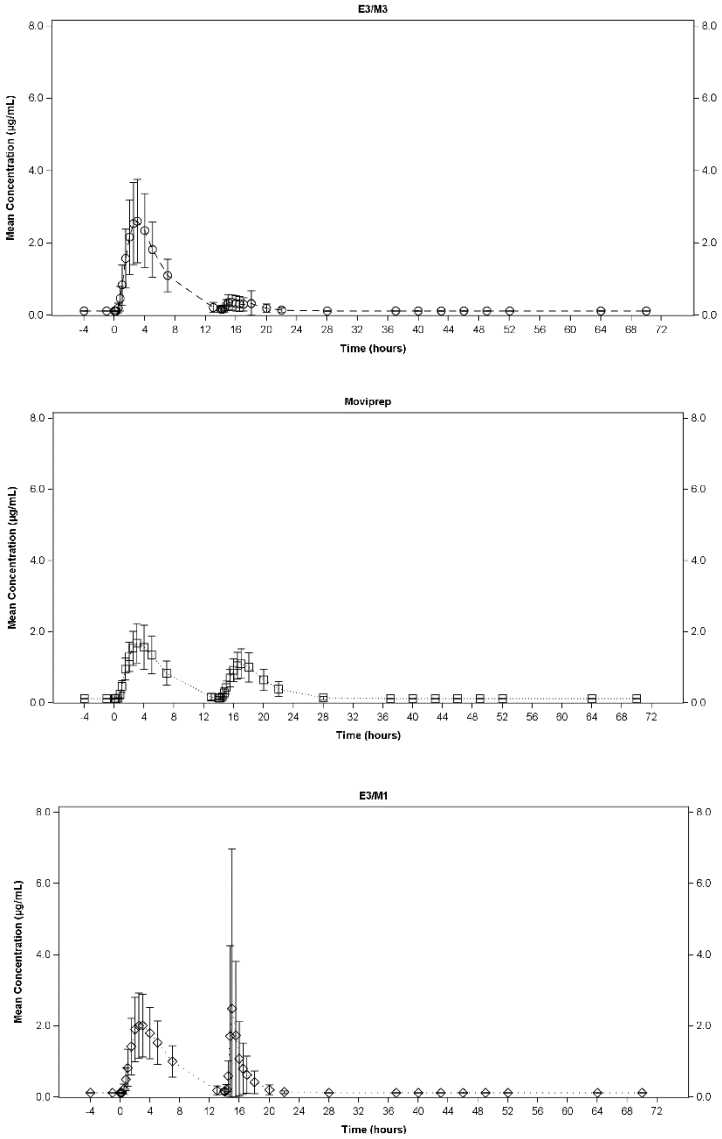
PK was only evaluated for the E3/M3, the E3/M1 and the MOVIPREP® group.

PEG3350:

PK of PEG3350 was assessed in blood and feces. However, analysis of PEG3350 in urine was not performed due to technical difficulties. The freeze and thaw cycle of the urine samples produced homogeneity problems, which was confirmed with incurred sample reproducibility analysis.

PEG3350 in Blood:

Figure 1: Mean Plasma PEG3350 Concentration-Time Profiles



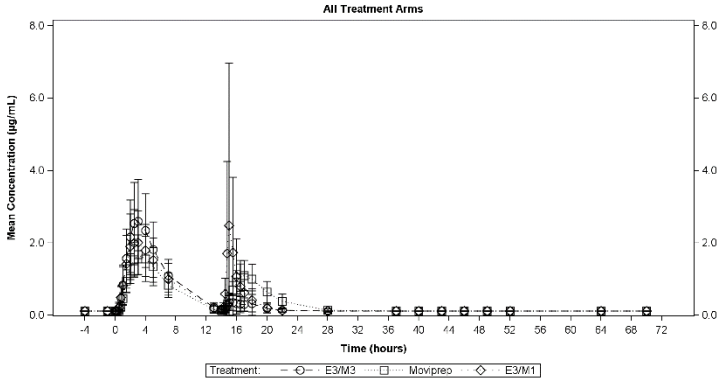


Table 7: Mean (SD) PK parameters for PEG3350 concentrations in blood

	E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
AUC(0-infinity) [(µg/ml)*h]	19.00 (7.633)	19.82 (7.991)	18.93 (7.677)
AUC(0-t_{last}) [(µg/ml)*h]	17.28 (7.192)	16.50 (5.607)	17.96 (7.564)
$t_{1/2}$ [h]	4.06 (2.340)	4.53 (5.433)	2.16 (1.257)
t_{max} [h]	3.01 (0.609)	3.78 (3.156)	6.43 (5.856)
CL [l/h]	8,923.2 (4,293.89)	11,310.1 (3,489.38)	8,727.4 (3,819.11)
CL/BW [l/(h*kg)]	131.80 (75.560)	181.46 (64.425)	129.83 (45.045)
V_d [l]	48,481.0 (29,810.83)	74,699.3 (110,227.41)	25,838.2 (14,898.10)
C_{max} [µg/ml]	2.706 (1.1699)	1.736 (0.5798)	3.604 (4.1461)
C_{max}/AUC(0-infinity) ratio [1/h]	0.1418 (0.02902)	0.0904 (0.02008)	0.1712 (0.11605)
lambda$_z$ [1/h]	0.2202 (0.10534)	0.2185 (0.07090)	0.3954 (0.15894)

PEG3350 in Feces:

Figure 2: Mean PEG Concentration in Faces for each study day

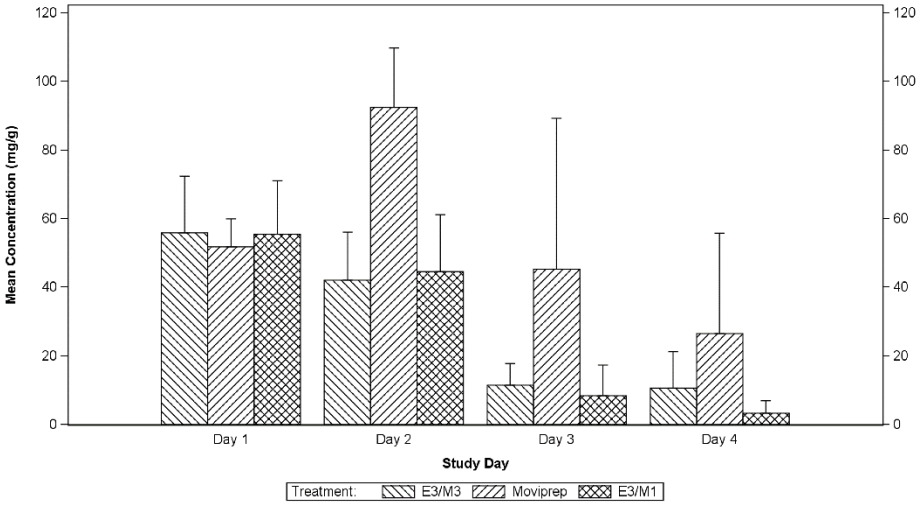


Table 8: Mean (SD) PEG3350 concentration (mg/g) in faeces for each study day of PK faeces sampling

	E3/M3 (N = 21)	MOVIPREP® (N = 20)	E3/M1 (N = 20)
Day 1	55.88 (16.515)	51.86 (8.155)	55.49 (15.646)
Day 2	42.03 (14.070)	92.56 (17.273)	44.59 (16.641)
Day 3	11.49 (6.319)	45.33 (43.923)	8.54 (8.871)
Day 4	10.66 (10.613)	26.51 (29.270)	3.39 (3.678)

Table 9: Mean (SD) Cumulative amount of PEG3350 (mg) of all post-dose faeces PK samples

E3/M3 (N = 21)	MOVIPREP® (N = 20)	E3/M1 (N = 20)
138,561.5 (49,096.15)	189,797.0 (19,146.71)	119,527.6 (16,152.74)

The amount of PEG3350 in faeces for each study day and the cumulative amount in feces was consistent with the amount of PEG administered in each group. The amount of PEG in Day 2 and accumulative amount of PEG in feces was highest in the MOVIPREP® group. This was to be expected according to the amounts of PEG3350 taken in the study group, as the subject who were administered the MOVIPREP® have received 200 g PEG3350 while subjects in E3/M3 and E3/M1 had received only 140 g of PEG3350.

Approximately 85% to 99% of the administered 140 g PEG3350 was recovered in feces following oral administration.

Table 10: Amount and percent of PEG 3350 recoveried in Urine and Feces

	E3/M3	E3/M1	Moviprep
Administered PEG Amount (g)	140	140	200
Amount in Urine (g)	NA	NA	NA
% in Urine	NA	NA	NA
Amount in Feces (g)	138.56	119.53	189.79
% in Feces	99.0%	85.4%	94.9%

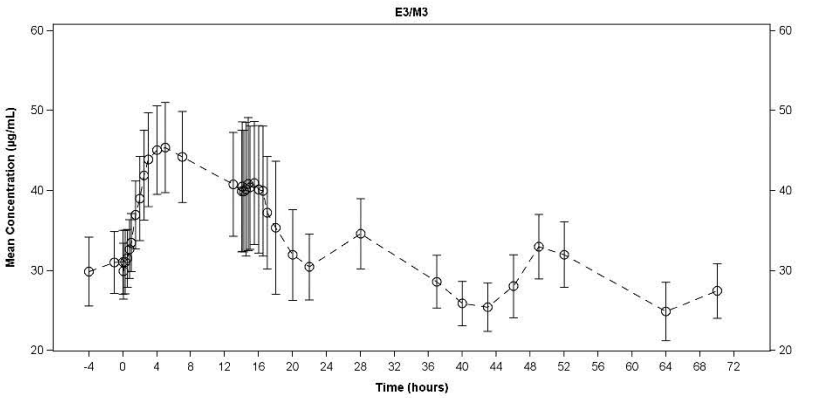
Note: Phase3/TBM formulation contains 140 g of PEG3350.

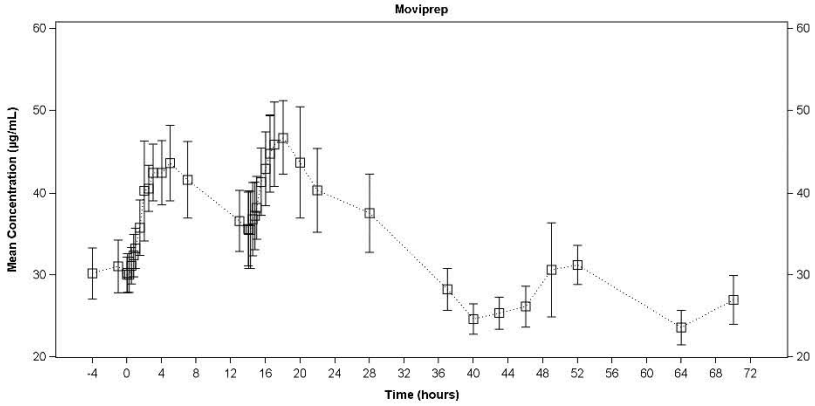
Sulphate:

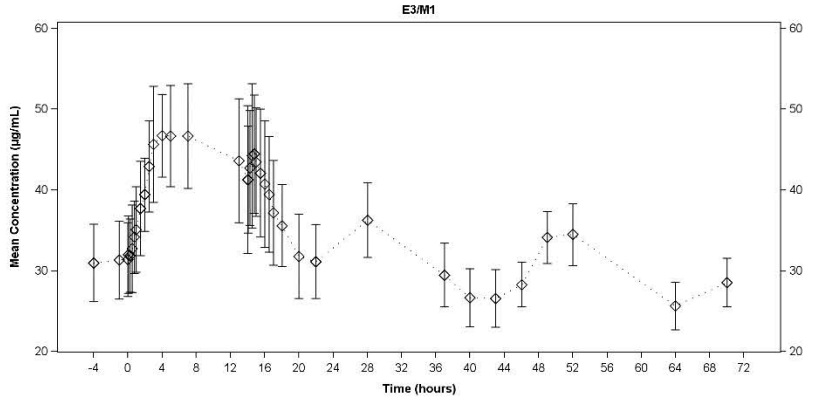
Sulphate in plasma:

The baseline plamsa sulfate level was approximately 30 ug/mL and baseline uncorrected sulfate Cmax was 48.05 (6.01: SD) ug/mL. Plasma sulfate level returns to its baseline level approximately 20 hour after the evening dose or 6 hours after the morning dose for E/M3 and E3/M1.

Figure 3: Mean plasma sulphate concentration-Time Profile


E3/M3
Mean Concentration (µg/mL)
Time (hours)


Moviprep
Mean Concentration (µg/mL)
Time (hours)


E3/M1
Mean Concentration (µg/mL)
Time (hours)

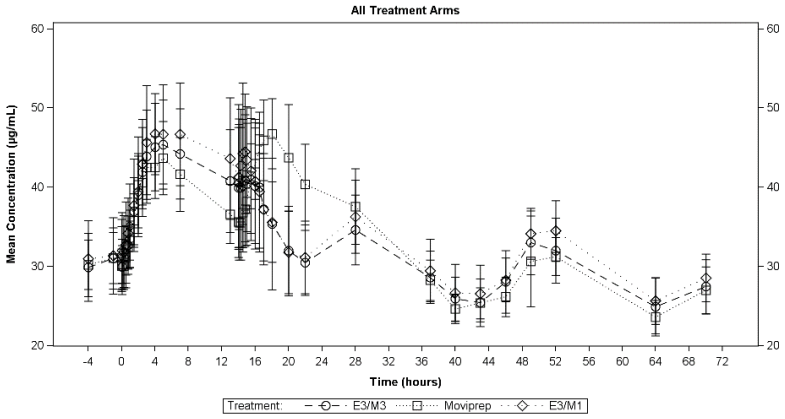


Table 11: Summary statistics for all PK parameters for baseline-corrected Sulfate concentrations

	E3/M3 (N = 21)		MOVIPREP® (N = 20)		E3/M1 (N = 20)	
	N_m	Mean (SD)	N_m	Mean (SD)	N_m	Mean (SD)
Sulphate						
AUC(0-infinity) [(µg/ml)*h]	2	0.3239 (0.16219)	1	0.5286 (0.52948)	3	0.2992 (0.15911)
AUC(0-t_{last}) [(µg/ml)*h]	0	206.20 (74.316)	0	260.33 (76.489)	2	225.72 (102.271)
$t_{1/2}$ [h]	2	10.519 (15.1886)	1	16.169 (24.0089)	3	5.478 (4.6503)
t_{max} [h]	0	8.08 (5.509)	0	14.31 (6.522)	2	9.65 (5.730)
CL [ml/h]	2	23,942.61 (12,295.980)	1	27,780.58 (11,578.624)	3	28,436.85 (20,950.321)
CL/BW [ml/(h*kg)]	2	363.50 (228.013)	1	435.08 (204.087)	3	435.62 (269.033)
V_d [l]	2	231.372 (205.4755)	1	369.806 (181.0701)	3	203.021 (210.3315)
C_{max} [µg/ml]	0	17.62 (4.796)	0	19.02 (4.708)	2	20.21 (6.856)
C_{max}/AUC(0-infinity) ratio [1/h]	2	0.06188 (0.017749)	1	0.05065 (0.020320)	3	0.08074 (0.031711)
$lambda_z$ [1/h]	2	0.22434 (0.264061)	1	0.10307 (0.069692)	3	0.30649 (0.266574)

N_m = number of missing values, N = number of subjects, E = evening dose, M = morning dose, SD = standard deviation

Sulphate in Urine:

Figure 4: Mean Sulphate Concentration in Urine for each study day

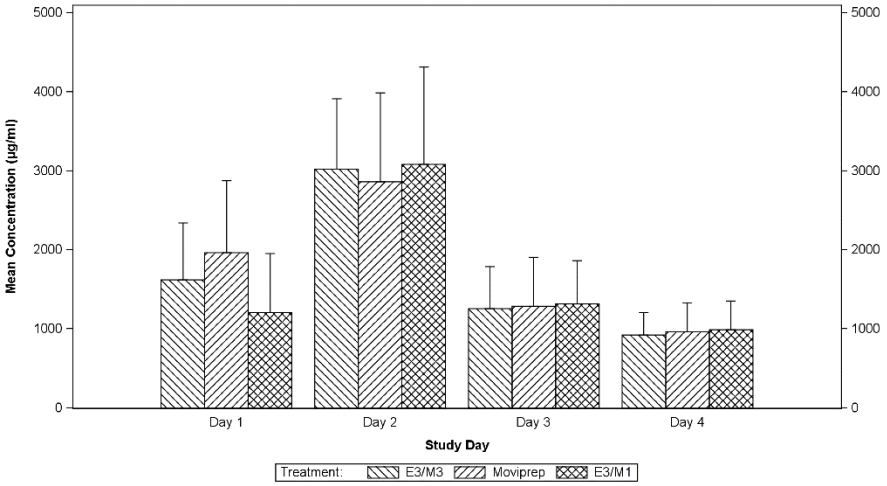


Table 12: Sulphate concentration in urine for each study day of PK urine sampling

	E3/M3 (N = 21)		MOVIPREP® (N = 20)		E3/M1 (N = 20)	
	N_m	Mean (SD)	N_m	Mean (SD)	N_m	Mean (SD)
			Sulphate [mg/dl]			
Day 1	0	162.32 (71.876)	0	196.93 (90.651)	2	121.10 (74.184)
Day 2	0	302.20 (89.141)	0	286.36 (111.998)	2	308.42 (122.738)
Day 3	0	125.79 (53.204)	0	128.96 (61.755)	2	131.56 (55.049)
Day 4	0	92.21 (28.541)	0	96.51 (36.724)	2	98.94 (36.489)

Table 13: Baseline-corrected cumulative amount of Sulphate of all post-dose urine PK samples

E3/M3 (N = 21)		MOVIPREP® (N = 20)		E3/M1 (N = 20)	
N_m	Mean (SD)	N_m	Mean (SD)	N_m	Mean (SD)
		Sulphate [mg]			
0	2,617.24 (2,134.188)	0	3,249.51 (1,745.065)	2	2,652.79 (1,757.962)

Sulphate in Feces:

Figure 5: Mean Sulphate Concentration in Faces for each study day

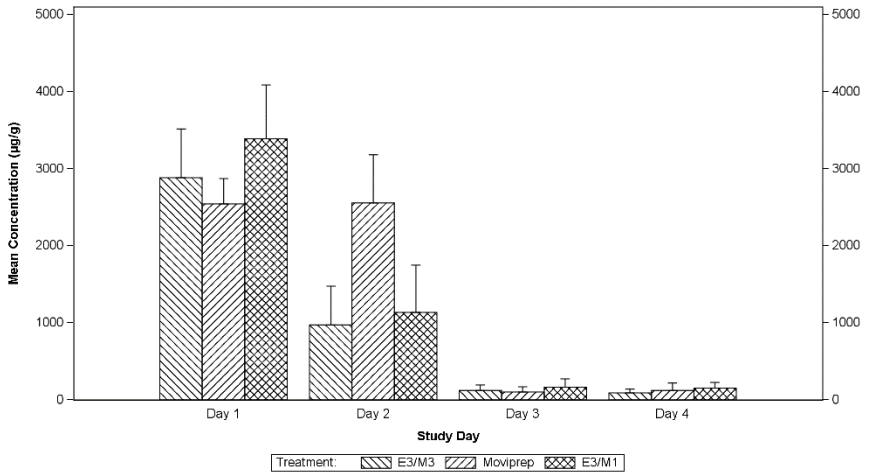


Table 14: Electrolyte concentration in faeces for each study day of PK faeces sampling

	E3/M3 (N = 21)		MOVIPREP® (N = 20)		E3/M1 (N = 20)	
	N_m	Mean (SD)	N_m	Mean (SD)	N_m	Mean (SD)
			Sulphate [µg/g]			
Day 1	0	2,882.06 (629.725)	0	2,541.36 (330.190)	0	3,388.73 (693.908)
Day 2	0	973.00 (502.284)	0	2,554.13 (626.438)	0	1,135.62 (614.598)
Day 3	11	120.81 (77.058)	11	107.00 (66.611)	14	165.15 (110.702)
Day 4	13	93.35 (47.592)	8	123.14 (98.416)	13	152.71 (75.520)

Table 15: Baseline-corrected cumulative amount of electrolytes of all post-dose faeces PK samples

E3/M3 (N = 21)		MOVIPREP® (N = 20)		E3/M1 (N = 20)	
N_m	Mean (SD)	N_m	Mean (SD)	N_m	Mean (SD)
		Sulphate [mg]			
0	4,168.63 (743.132)	1	7,354.89 (870.454)	1	4,454.49 (599.642)

Following oral administration of 9 g of sodium sulfate, about 69%-76% are recovered in feces and about 43% is recovered in urine.

Table 16: Amount and percent of sulfate recoveried in Urine and Feces

	E3/M3	E3/M1	Moviprep
Administered Sodium Sulfate Amount (g)	9	9	15
Amount of Sulfate (g)	6.08	6.08	10.14
Amount in Urine (g)	2.617	2.652	3.249
% in Urine	43.0%	43.6%	32.0%
Amount in Feces (g)	4.168	4.454	7.354
% in Feces	68.6%	73.3%	72.5%

Note: Phase3/TBM formulation contains 9 g of Sodium Sulfate.

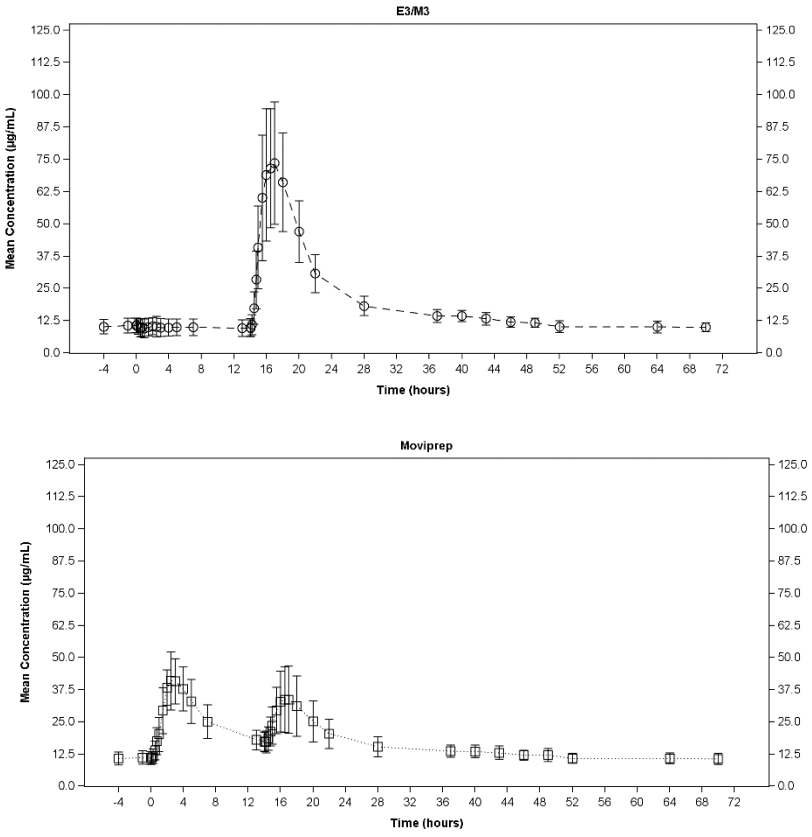
Ascorbic Acid:

Ascorbic Acid in Plasma:

The baseline plamsa ascorbic acid concentration was approximately 12 ug/mL and baseline uncorrected ascobbic acid Cmax was 81.18 (223.52 SD) ug/mL. Plasma ascorbic acid was return to its baseline level approcimately 36 hour after after the evening dose or 22 hours after the morning dose of the interim formulation (E/M3).

In all three groups, the plasma ascorbic acid concentration-time profile corresponded well with the amount and time of ascorbic acid administration.

Figure 6: Mean plasma Ascorbic Acid Concentration-Time Profile



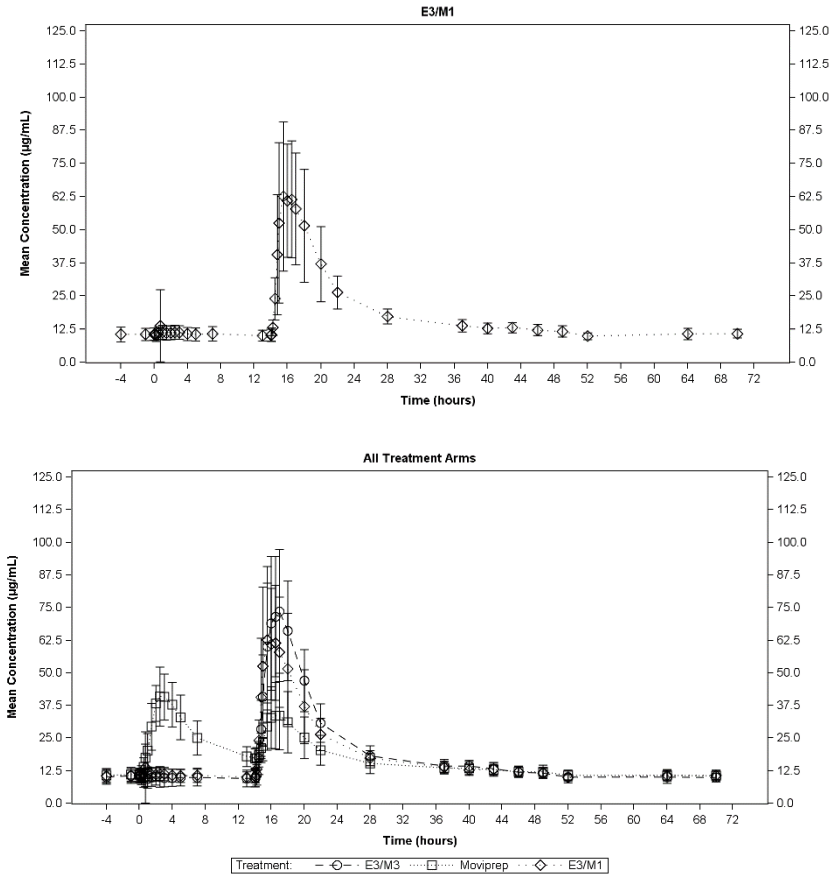


Table 17: Summary statistics for all PK parameters for baseline-corrected ascorbic acid concentrations

	E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
AUC(0-infinity) [(µg/ml)*h]	510.86 (132.394)	474.48 (255.934)	437.80 (176.698)
AUC(0-t_{last}) [(µg/ml)*h]	433.09 (157.290)	435.90 (232.981)	411.69 (174.073)
$t_{1/2}$ [h]	7.21 (6.157)	8.22 (5.033)	6.19 (3.353)
t_{max} [h]	16.77 (0.752)	6.95 (6.667)	15.32 (3.482)
CL [l/h]	107.39 (40.415)	35.18 (61.630)	135.86 (61.709)
CL/BW [l/(h*kg)]	1.66 (0.737)	0.64 (0.780)	2.13 (1.059)
V_d [l]	1,026.24 (675.063)	310.08 (726.461)	1,089.21 (462.280)
C_{max} [µg/ml]	70.82 (22.365)	33.36 (10.317)	60.88 (29.092)
C_{max}/AUC(0-infinity) ratio [1/h]	0.1427 (0.03139)	0.0659 (0.05422)	0.1410 (0.03546)
$lambda_z$ [1/h]	0.1356 (0.06364)	0.1099 (0.05019)	0.1363 (0.05554)

Ascorbic Acid in Urine:

Figure 7: Mean Ascorbic Acid Concentration in Urine for each study day

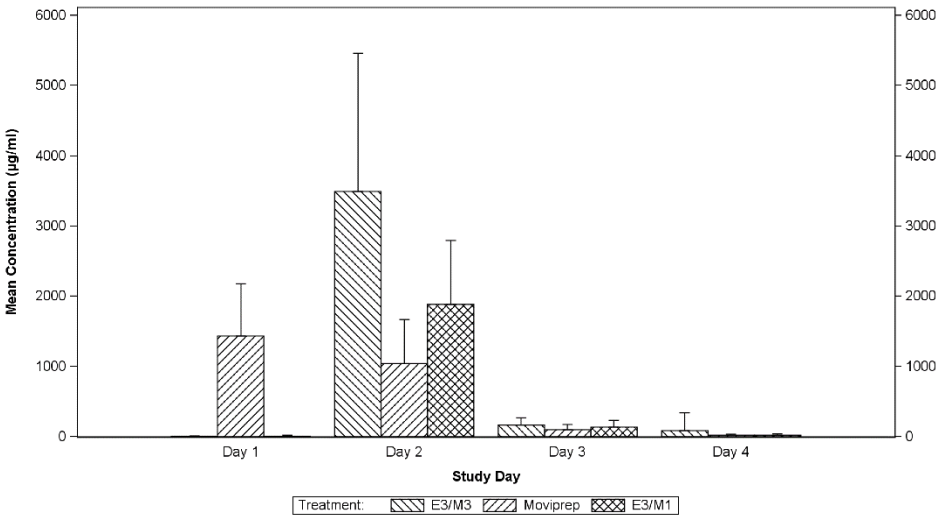


Table 18: Mean (SD) Ascorbic acid concentration [ug/ml] in urine for each study day of PK urine sampling

	E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
		Ascorbic acid	
Day 1	8.55 (7.618)	1,434.18 (745.513)	10.72 (10.166)
Day 2	3,493.84 (1,966.798)	1,040.72 (630.599)	1,886.34 (909.251)
Day 3	172.56 (100.798)	103.66 (71.633)	142.10 (90.316)
Day 4	85.65 (254.487)	24.28 (15.076)	26.16 (20.376)

Table 19: Mean (SD) Baseline-corrected cumulative amount of ascorbic acid (mg) of all post-dose urine PK samples

E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
	Ascorbic acid	
2,757.90 (1443.186)	1,676.71 (535.804)	1,428.92 (563.618)

Ascorbic Acid in Feces:

Figure 8: Mean Ascorbic Acid Concentration in Faces for each study day

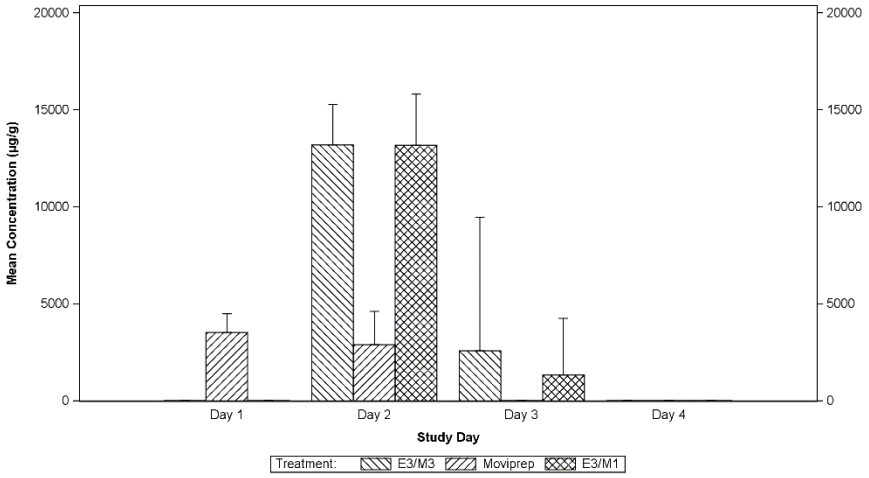


Table 20: Ascorbic acid concentration in faeces (ug/g) for each study day of PK faeces sampling

	E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
		Ascorbic acid	
Day 1	20.00 (0.000)	3,533.28 (972.154)	20.00 (0.000)
Day 2	13,215.10 (2,064.688)	2,903.86 (1,722.681)	13,172.36 (2,657.664)
Day 3	2,575.50 (6,887.462)	20.00 (0.000)	1,328.00 (2,924.777)
Day 4	20.00 (0.000)	20.00 (0.000)	20.00 (0.000)

The time and the amount of ascorbic acid recovered in urine and feces in each day corresponds well with the amount and time of ascorbic acid administration.

Table 21: Baseline-corrected cumulative amount (mg) of ascorbic acid of all post-dose faeces PK samples

E3/M3 (N = 21)	**MOVIPREP® (N = 20)**	**E3/M1 (N = 20)**
	Ascorbic acid	
34,431.82 (8,559.635)	9,772.16 (4,269.752)	27,196.34 (12,909.298)

Following oral administration of 33.9 g sodium ascobate and 20.1 g ascobic acid (E3/M3 which has the most similar content compared to Phase3/TBM formulation), about 68.5% was recovered in feces and 5.5% was recovered in urine.

Table 22: Amount and percent of ascobic acid recoveried in Urine and Feces

	E3/M3	E3/M1	Moviprep
Administered Sodium Ascorbate Amount (g)	33.9	56.6	11.8
Administered Ascorbic Acid Amount (g)	20.1		9.4
Amount of total ascobic acid (g)	50.23	50.3	19.89
Amount in Urine(g)	2.76	1.43	1.68

% in Urine	5.5%	2.8%	8.4%
Amount in Feces (g)	34.43	27.196	9.77
% in Feces	68.5%	54.1%	49.1%

Note: Phase3/TBM formulation contains 48.11 g of Sodium Ascorbate and 7.54 g Ascorbic acid

Oxalic Acid:

Oxalic Acid in Plasma:

Oxalic acid in blood was below the lower limit of quantification.

Oxalic Acid in Urine:

Figure 9: Mean Oxalic Acid Concentration in Urine for each study day

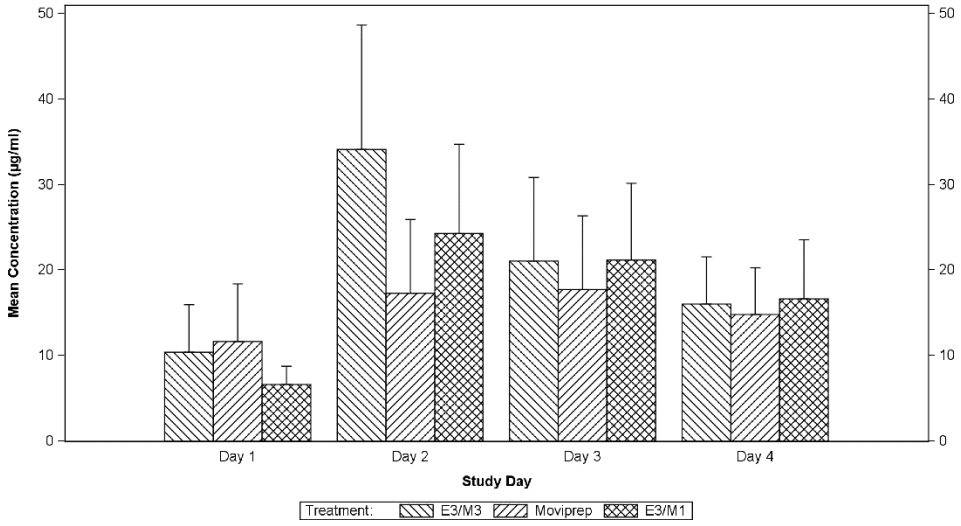


Table 23: Mean (SD) Oxalic acid concentration (ug/ml) in urine for each study day of PK urine sampling

	E3/M3 (N = 21)	MOVIPREP® (N = 20)	E3/M1 (N = 20)
		Oxalic acid	
Day 1	10.40 (5.593)	11.70 (6.690)	6.61 (2.169)
Day 2	34.09 (14.540)	17.34 (8.558)	24.29 (10.436)
Day 3	21.10 (9.716)	17.76 (8.572)	21.20 (8.979)
Day 4	16.06 (5.481)	14.83 (5.449)	16.67 (6.873)

Table 24: Mean (SD) Baseline-corrected cumulative amount of oxalic acid (mg) of all post-dose urine PK samples

E3/M3 (N = 21)	MOVIPREP® (N = 20)	E3/M1 (N = 20)
	Oxalic acid	
35.35 (46.310)	25.77 (31.802)	28.09 (26.777)

Oxalic Acid in Feces:

Figure 10: Mean Oxalic acid Concentration in Faces for each study day

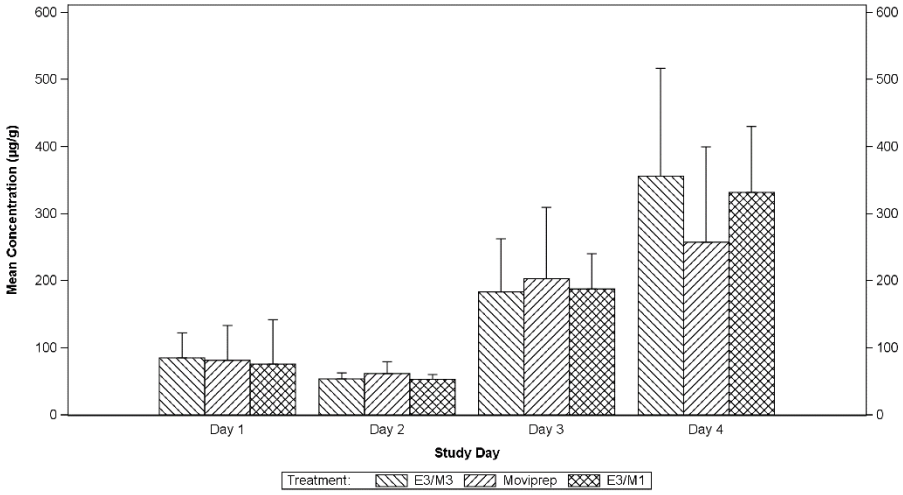


Table 25: Oxalic acid concentration in faeces (ug/g) for each study day of PK faeces sampling

	E3/M3 (N = 21)	MOVIPREP® (N = 20)	E3/M1 (N = 20)
		Oxalic acid	
Day 1	85.05 (37.748)	81.85 (51.260)	75.90 (66.308)
Day 2	54.05 (8.943)	61.75 (17.647)	53.53 (7.269)
Day 3	183.60 (79.245)	203.08 (106.624)	188.00 (52.577)
Day 4	356.25 (160.400)	257.58 (141.850)	331.71 (98.737)

Excretion of oxalic acid in urine and feces were relatively delayed and prolonged (Day 2 through Day 4 in urine and Day 3 to Day 4 in feces) compared to that of ascorbic acid (majority excreted on Day 2 in both urine and feces) or PEG 3350 (majority excreted on Day 1 to Day 2 in feces) reflecting the slow formation of oxalic acid despite unmreaurable plasma concnetration.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haemotology, clinical chemistry, urinalysis) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring.

- According to the sponsor, there was no death or discontinuation due to treatment-emergent adverse events (TEAEs) during the study.
- The majority of subjects reported good to acceptable tolerance of the solution, regardless of the treatment group. However, most subjects experienced symptoms of some kind; the most common ones were nausea, vomiting, abdominal discomfort and abdominal pain.
- More than three quarters of all TEAEs in both parts of the study were related to the study medication.

Table 26: Summary of TEAEs for Part A

	E2/M3 (N = 20)		E3/M3 (N = 21)		E-IP/M3 (N = 20)		MOVIPREP® (Evening and Morning) (N = 20)	
	n	%	n	%	n	%	n	%
Number of subjects with AE	19	95.0%	19	90.5%	16	80.0%	20	100.0%
Number of symptoms (MedDRA Codes)	60		59		73		67	
Number of episodes	60		59		73		67	
Maximal intensity								
Mild	44	73.3%	39	66.1%	48	65.8%	49	73.1%
Moderate	9	15.0%	18	30.5%	23	31.5%	15	22.4%
Severe	7	11.7%	2	3.4%	2	2.7%	3	4.5%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Relationship to study treatment								
Probable	46	76.7%	46	78.0%	54	74.0%	57	85.1%
Possible	0	0.0%	5	8.5%	5	6.8%	2	3.0%
Unrelated	14	23.3%	8	13.6%	14	19.2%	8	11.9%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Table 27: Summary of TEAEs for Part B

	E3/M1/ (N = 20)		E3/M4 (N = 20)		E3/M5 (N = 20)		E3/M-IP (N = 20)	
	n	%	n	%	n	%	n	%
Number of subjects with AE	14	70.0%	18	90.0%	20	100.0%	15	75.0%
Number of symptoms (MedDRA Codes)	42		54		68		39	
Number of episodes	42		54		68		39	
Maximal intensity								
Mild	32	76.2%	43	79.6%	52	76.5%	30	76.9%
Moderate	7	16.7%	10	18.5%	13	19.1%	8	20.5%
Severe	3	7.1%	1	1.9%	3	4.4%	1	2.6%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Relationship to study treatment								
Probable	35	83.3%	47	87.0%	58	85.3%	28	71.8%
Possible	1	2.4%	1	1.9%	5	7.4%	1	2.6%
Unrelated	6	14.3%	6	11.1%	5	7.4%	10	25.6%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Reviewer's Conclusion: Based on the PD result of OUT study, formulation E3 and M1 were identified as the optimal evening and morning formulations.

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/s/

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04/30/2018

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