Summary of Clinical Study Report

NER1006-01/2012 (OPT)

Pharmacodynamic and clinical evaluation of dose and taste-optimised low volume PEG-based bowel cleansing solutions using the split-dosing intake regimen in healthy subjects and in subjects undergoing screening colonoscopy

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Clinical Phase: Phase II

Study Dates: 22 October 2012 (first subject informed consent) to 08 July 2013 (last subject last visit date)

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1 SYNOPSIS AND STUDY ABSTRACT

Name of Company: Norgine Ltd **Name of Active Substance(s):** PEG3350, sodium sulfate, sodium ascorbate, ascorbic acid, sodium chloride, potassium chloride	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use only)
Title: Pharmacodynamic and clinical evaluation of dose and taste-optimised low volume PEG-based bowel cleansing solutions using the split-dosing intake regimen in healthy subjects and in subjects undergoing screening colonoscopy		
Principal Investigator: [redacted]		
Study centre: PAREXEL International GmbH, [redacted] Germany		
Publication (reference): None		
Study period: 22 October 2012 (first subject informed consent) to 08 July 2013 (last subject last visit date)	**Clinical Phase:** II	
Objectives of the study: The objectives of the study were to investigate the effects of dose and taste-optimised, low volume polyethylene glycol (PEG)-based formulations after split-dosing, on stool output in healthy subjects, and on stool output and bowel cleansing quality in subjects undergoing a screening colonoscopy. The safety and tolerability of the optimised formulations were assessed and compared with MOVIPREP®, a commercially available reference bowel preparation. This study also aimed to assist in the identification of the optimal treatment regimen prior to further investigations.		
Methodology: This was an open-label, randomised, Phase II study with two sequential parts (A and B) to investigate the pharmacodynamics (PD) (stool weight) and tolerability in Parts A and B, and clinical efficacy and pharmacokinetics (PK) (in Part B only) of dose and taste-optimised low volume PEG-based bowel cleansing solutions. MOVIPREP® acted as the reference product. There were four treatment arms in each part of the study, to which subjects were randomised in a 1:1:1:1 ratio, separately for each part. Study treatment was administered on Day 1 (evening dose) and on Day 2 (morning dose). Following written informed consent, subjects were screened not more than a month before the first dose of investigational medicinal product (IMP). After screening (Days -30 to -1), the study was scheduled for 2 days per subject. Subjects were confined to the clinical unit from the morning of Day 1 to the evening of Day 2 (approximately 18:00). In the morning of Day 2, subjects in Part B were transferred to a colonoscopy suite for the conduct of their colonoscopy, after which they were returned to the clinical unit.		
Number of subjects (planned and analysed): It was planned to randomise/enrol a total of 240 subjects in the study, to achieve at least 200 evaluable cases in total across both parts of the study. In each of Part A and Part B, a sufficient number of subjects were screened to allow 120 subjects to be randomised/enrolled to each part. At least 30 subjects were enrolled per treatment arm to achieve 25 evaluable subjects per treatment arm (at least 100 evaluable		

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cases in each part).

In Part A of the study, 120 subjects were included, three of whom were prematurely withdrawn from the study. In Part B of the study, 120 subjects were included, all of whom completed the study according to protocol.

Diagnosis and main criteria for inclusion:

Subjects who met the following criteria were considered eligible to participate in the study:

- The subject's written informed consent had to be obtained prior to inclusion.
- Subjects aged 40 to 70 years.
- Part B only: subjects who were willing to undergo a screening colonoscopy.
- Part A only: subjects who were without any history of clinically significant gastrointestinal (GI) symptoms by clinical judgement and without the presence of acute abdominal discomfort or symptoms.
- Females of child bearing potential had to be surgically sterile, postmenopausal, practicing true sexual abstinence or using an acceptable form of effective contraception throughout the study.
- Ferrous sulphate should have stopped at least one week prior to study medication.

Subjects who met the following main criteria were not included in the study:

- Part A only: subjects undergoing screening colonoscopy.
- Presence of current clinically significant functional GI disorder (e.g., gastric emptying disorder, chronic constipation, irritable bowel syndrome [IBS]).
- Regular use of laxatives or colon motility altering drugs in the last month.
- Any history or current presence of ileus, GI obstruction or perforation, GI tract cancer, inflammatory bowel disease (IBD) or colonic resection.
- History or evidence of any clinically significant cardiovascular or neurological disease, cardiac, renal or hepatic insufficiency.
- Clinically relevant findings on physical examination or clinically relevant deviations of laboratory parameters from reference ranges.

Test products, dose, batch N°:

Powder for oral solution, reconstituted with water, containing different amounts of PEG3350, sodium sulfate, sodium chloride, potassium chloride, sucralose, aspartame, artificial fruit punch flavour, orange flavour, citric acid, sodium ascorbate and/or ascorbic acid, were administered as different treatment regimens in each arm, with additional intake of specified volumes of clear fluid.

The specific doses and batch numbers are included as part of the main text in this clinical study report in Section 9.4.1.

The formulations were labelled and administered as follows in each treatment arm:

Part A, Arm 1 – OPT001: evening dose = TF048; morning dose = TF043
Part A, Arm 2 – OPT002: evening dose = TF043; morning dose = TF048
Part A, Arm 3 – OPT003: evening dose = TF047; morning dose = TF043

Part B, Arm 1 – OPT003: evening dose = TF047; morning dose = TF043

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Part B, Arm 2 – OPT007: evening dose = TF047; morning dose = TF043 (additional clear fluid for each dose differed from Arm 1, i.e., it was 1000 mL in Arm 1 and 500 mL in Arm 2)
Part B, Arm 3 – OPT006: evening dose = TF047; morning dose = TF044

Duration of treatments:
Study treatment was administered on Day 1 (evening dose) and on Day 2 (morning dose).

Reference therapy, dose and mode of administration, batch number:
Powder for oral solution, reconstituted with 1000 mL water, containing PEG3350, sodium sulfate, sodium chloride, potassium chloride, lemon flavour and sweetener, sodium ascorbate and ascorbic acid, was administered, with additional intake of 500 mL clear fluid. The specific doses and batch numbers are included as part of the main text in this clinical study report in Section 9.4.1.
The formulation was labelled as OPT004 (MOVIPREP®) and administered as Arm 4 (evening and morning dose) in each of Part A and Part B of the study.

Criteria for evaluation:
As primary variables, the following parameters were determined:
Part A, Primary variable:
- Stool weight output generated from the start of IMP 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 IMP 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©).

As secondary variables, the following parameters were determined:
Part A
- Tolerability (vomiting rate).
- Time and volume of IMP to reach a clear effluent.

Part B
- Tolerability (vomiting rate).
- The segmental cleansing scores for each of the five colon segments.
- Time and volume of IMP to reach a clear effluent.
- Pharmacokinetic evaluation of key active ingredients: ascorbate components and their metabolite (oxalic acid), and electrolytes (sodium, potassium and chloride) in plasma, urine and faeces, and PEG3350 in faeces, at defined time points, to demonstrate biological activities. Electrolytes (sodium, potassium and chloride) in blood and urine were quantified using clinical chemistry methods.

The following safety parameters were assessed: adverse events (AEs), safety laboratory tests, cardiovascular parameters (electrocardiogram [ECG], blood pressure, and heart rate), body weight, physical examination, and tolerability using a subject questionnaire (including the assessment of predefined symptoms).

Statistical methods:
Stool weight results were listed and summarised descriptively; graphical representations of

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the results were also presented. A statistical analysis was performed to compare the mean of the stool weight against 2750 g for each treatment. A parametric statistical analysis was performed using a one-sample t-test by treatment.

Results for cleansing success rate and segmental cleansing score were listed and summarised descriptively. A pair wise Fisher's exact test was performed to determine if there were significant differences between the treatments relative to MOVIPREP®.

Incidences of vomiting were listed and summarised. A pair-wise Fisher's exact test was performed to determine if there were significant differences between the treatments relative to MOVIPREP®.

Results for the time taken and volume of IMP consumed in order to reach clear effluent were listed and summarised descriptively.

Pharmacokinetic concentrations and parameters for plasma, urine and faeces data were listed and summarised descriptively. Graphical representations of the plasma concentration data were also presented. A sensitivity analysis was performed on all PK concentrations in plasma for each time point and for all amounts excreted in each time interval for urine and faeces, as well as on all PK parameters. This sensitivity analysis was performed to present the effect that implausible values have on the PK results. Outliers were identified as any value more than 1.5 interquartile ranges below the first quartile or above the third quartile.

Safety data were listed and summarised appropriately. No formal statistical testing was performed on the safety results.

SUMMARY – CONCLUSIONS

Pharmacodynamics:

From the results obtained from the statistical analysis on the overall stool weight, the null hypothesis can only be rejected for OPT002 and OPT003 in Part A and OPT003 and OPT007 in Part B. It can therefore be concluded that the overall stool weight output during the 24-hour period for OPT002 and OPT003 in Part A and OPT003 and OPT007 in Part B was more than 2750 g.

In general, most subjects reached clear effluent (e.g., 90% of subjects in the OPT003 group) with only OPT004 in Part A having more than 50% of censored subjects. Almost all subjects had a successful cleansing score in Part B, with 77 to 83% across the treatment groups reaching clear effluent compared to 63% in the comparator group, OPT004. While there is no direct relationship between clear effluent and cleansing success, there is a trend towards a positive association between the two observations.

Clinical Evaluation (Part B):

For cleansing success rate and segmental cleansing scores, the Fisher's exact test performed to determine whether there were any significant differences between the treatments relative to OPT004 resulted in p-values all larger than the specified alpha level of 0.05 for this study. Although these p-values were not statistically significant, because their exact values were relatively close to each other, it can be concluded that there were no significant differences between the treatments in terms of overall cleansing success. It should be noted that OPT003 and OPT007 had 100% cleansing success rate. Furthermore, in terms of segmental cleansing, the scores assigned to OPT003, OPT007 and OPT006 for all colon segment assessments were higher than the scores assigned to OPT004. Overall only six subjects did not have cleansing success, and three of those were in the OPT004 treatment arm.

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Pharmacokinetics (Part B):

Plasma:

Plasma ascorbic acid was higher in OPT004 on Day 1 compared to the other treatments. Several subjects administered OPT003, OPT007 and OPT006 had low concentrations of ascorbic acid measured in the plasma samples following the Day 1 treatment. As ascorbate components were not present in the OPT003, OPT007 and OPT006 treatments on Day 1, measurement of ascorbic acid in plasma in Day 1 samples was likely due to ascorbic acid already present from other sources prior to treatment. On Day 2, the ascorbic acid concentrations were higher in OPT003, OPT006 and OPT007 compared to OPT004; this was as expected as OPT003, OPT006 and OPT007 had more ascorbate components in the Day 2 morning dose.

Oxalic acid was below the level of quantification in plasma for all subjects on all treatments.

Urine:

As observed in plasma, the ascorbic acid amounts excreted in urine were lower on Day 1 for OPT003, OPT006 and OPT007 compared to OPT004; this is likely because OPT004 was the only treatment to contain ascorbate components in the evening dose. On Day 2, the amount excreted was higher in OPT004 then for the other treatments. The oxalic acid amount excreted was consistent for all treatments across the two treatment days.

Chloride and potassium amount excreted were consistent for all treatments across the two treatment days as expected given the treatments all contained similar levels of chloride and potassium.

Sodium amount excreted in urine was consistent for all treatments on Day 1 but slightly higher for OPT004 following the Day 2 morning dose.

Faeces:

The PEG3350 amount excreted in faeces was consistent across the treatment groups on Day 1 as expected, as all treatments contained 100 g PEG3350. On Day 2 OPT003, OPT006 and OPT007 amount excreted were consistent, and OPT004 amount excreted was higher, as expected as the other treatments only had 40 g PEG3350 in the Day 2 morning dose compared to 100 g for OPT004.

Similar to the plasma and urine PK results for Day 1, ascorbic acid amount excreted in faeces was lower for the OPT003, OPT007 and OPT006 treatments compared to OPT004, after removing the outlier from the analysis. On Day 2, the amount excreted was comparable to Day 1 for OPT004 and was considerably lower than that measured for the other treatments.

The amount excreted for oxalic acid after outlier removal was consistent as it was for chloride, potassium and sodium across all the treatment groups on the two dosing days.

Overall, exposures observed for the separate components of each of the treatments were not significantly different, with only slight variations, as expected, where there were composition differences between the four treatments.

Safety and Tolerability:

The incidence of treatment-emergent adverse events (TEAEs) was similar amongst treatment groups for both Part A and Part B. Most of the TEAEs were assessed as related to the IMP, and of mild intensity. Only three subjects were excluded from the study (Part A) based on

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TEAEs and no serious adverse events (SAEs) or deaths were reported during the study. Compared to OPT004 (MOVIPREP®), the different treatment regimens of the IMP were well tolerated and no safety issues were reported during the study. OVERALL CONCLUSIONS: The overall stool weight output during the 24-hour period for OPT002 and OPT003 in Part A and OPT003 and OPT007 in Part B was more than 2750 g. Cleansing success rate in Part B of the study was very high, with OPT003 and OPT007 having a 100% cleansing success rate. In terms of segmental cleansing, scores assigned to OPT003, OPT007 and OPT006 for all colon segment assessments were higher than the scores assigned to OPT004. The overall conclusion from the safety analysis on IMP administered during this study is that there are no safety concerns.		
Date of the report: Final 1.0, 31 January 2014		