2 SYNOPSIS

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

Title of study A multi-centre, randomised, investigator-blinded study comparing the polyp detection rate of two different types of bowel preparation: a 2-litre solution (MOVIPREP®) versus a hyperosmotic and stimulant combined low volume bowel preparation (Sodium Picosulfate and Magnesium Citrate)	
EudraCT-No. 2011-002364-25	
Coordinating Investigator [redacted] Klinikum Aschaffenburg, [redacted] [redacted] Germany	
Publication (reference) Not applicable	
Studied period 11 Nov 2011 to 28 Jan 2013	Phase of development IV
Objectives 1. To compare the polyp and adenoma detection rate of MOVIPREP® versus an oral Sodium Picosulfate/Magnesium Citrate solution 2. To assess the correlation between the cleansing quality and the detection rate of the two types of bowel cleansing preparations.	

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Methodology

This was a multi-centre, randomised, investigator-blinded interventional study in outpatients and in-patients undergoing a morning colonoscopy. Blinding was maintained by assignment of an Investigator responsible for dispensing the Investigational Medicinal Product (IMP) and assessing Adverse Events (AEs) and an independent and blinded gastroenterologist to perform the colonoscopy and efficacy assessments. Bowel cleansing was performed using a course of either 2 litres of MOVIPREP® bowel lavage solution with 1 litre (or more) of extra clear liquids, or 2 x 150 mL of oral Sodium Picosulfate/Magnesium Citrate preparation followed by 250 mL clear liquid per hour before a morning colonoscopy.
Each participating centre used both types of preparation according to the randomisation list.

Study duration

Each patient recruited into the study was treated once with either MOVIPREP® or an oral Sodium Picosulfate/Magnesium Citrate preparation (CitraFleet®). Patients underwent bowel cleansing prior to colonoscopy starting the day before the procedure, according to the presently recommended instructions for MOVIPREP® or CitraFleet®. Recruited patients received study medication at the screening visit and were given detailed intake instructions. The scheduled colonoscopy was performed within 30 days after the screening visit. The end of treatment assessment was conducted after completion of the colonoscopy procedure when the patient was ready to leave the endoscopy unit.

Administration of MOVIPREP®

- Day -1: In the afternoon/evening (up to 11 p.m.): 1 litre MOVIPREP® solution followed by at least 0.5 litres of clear liquid.
- Day 0: (day of colonoscopy) from 5 a.m. onwards: 1 litre MOVIPREP® solution followed by at least 0.5 litres of clear liquid.
- There had to be a minimum period of 1 hour, preferably at least 2 hours, between

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Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

the end of the intake of the second dose of the bowel cleansing solution and the beginning of the colonoscopy.

Each litre was drunk within 1 to 1.5 hours followed by at least 0.5 litre of any additional clear liquid, which included water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee (without milk).

Administration of CitraFleet®

- Day -1 (morning): 150 mL CitraFleet® solution followed by 250 mL clear liquid per hour to avoid dehydration while the washout effect persists.
- Day -1: (afternoon): 150 mL CitraFleet® solution followed by 250 mL clear liquid per hour to avoid dehydration while the washout effect persists.
- The morning dose was to be taken at about 7 a.m., the afternoon dose between 2 p.m and 4 p.m.
- There was no administration of CitraFleet® on the day of colonoscopy.

The gastroenterologist performing the colonoscopy ensured that the planned colonoscopy was performed according to the time schedule given above.

Primary endpoint

Polyp detection rate (PDR) defined as number of patients with at least one polyp or flat lesion as recorded by the endoscopist.

Key secondary endpoint

Adenoma detection rate (ADR) defined as number of patients with at least one adenoma as confirmed by the pathologist.

Additional secondary endpoints

- ADR and PDR by location:
  - Left-sided (rectum, colon sigmoideum, colon descendens, left half of colon transversum),
  - Right-sided (right half of colon transversum, colon ascendens, caecum).

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- Cancer detection rate, defined as number of patients with at least one malignancy in relation to the total analysis population.
- Flat lesion only detection rate.
- Advanced risk lesion detection rate (lesions > 1 cm, low grade and/or villous).
- Colonoscopy completion rate.
- Colon cleansing quality, as reported by the gastroenterologist, according to the Harefield Cleansing Scale©.
- Acceptability and tolerability of the study medication.

Number of patients (planned and analysed)

Planned: 400 patients with completed colonoscopy (200 MOVIPREP® and 200 CitraFleet®) were planned to be included for the scheduled interim analysis; a maximum of up to 800 patients were planned to be included in the study after adaptation of the sample size based on the results of the interim analysis.

Analysed: 398 evaluable cases (safety population)

Diagnosis and criteria for inclusion

Inclusion criteria:

(1) Patient's written informed consent must be obtained prior to inclusion.

(2) Male or female outpatients or inpatients aged 40 to 80 years willing to undergo a colonoscopy for:
- Diagnostic or surveillance purposes
  or
- Screening purposes where patient
  a. Has a known personal or familial risk of colon neoplasia,
     or
  b. Is aged 55 - 80, willing to undergo a screening colonoscopy.

(3) Willing, able and competent to complete the entire procedure and to comply with study instructions.

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
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Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

(4) Females of childbearing potential must employ an adequate method of contraception.

Main exclusion criteria:

(1) History of gastric emptying disorders.
(2) History of ileus, toxic megacolon, gastrointestinal obstruction and colonic perforation.
(3) History of phenylketonuria.
(4) Known glucose-6-phosphate dehydrogenase deficiency.
(5) Known hypersensitivity to macrogol 3350, sodium sulphate or ascorbic acid/sodium ascorbate.
(6) History of colonic resection.
(8) Presence of congestive heart failure (NYHA III + IV).
(9) Acute life-threatening cardiovascular disease.
(10) Documented history of severe renal insufficiency (creatinine clearance <30 mL/min).
(11) Other contraindication described in the summary of product characteristics (SmPC) of either preparation.

Test product, dose and mode of administration, batch number

MOVIPREP® containing 100 g PEG 3350, 7.5 g sodium sulphate with 4.7 g ascorbic acid and 5.9 g ascorbate, electrolytes (2.691 g NaCl, 1.015 g KCl), 0.340 g lemon flavour and sweetener (aspartame-acesulfame).
Batch number: MOVIPREP® pack: 144099 (sachet A: 148473; sachet B: 146860)

Duration of treatment

MOVIPREP® was administered on Day -1 (evening dose) and on Day 0 (morning dose).
CitraFleet® was administered on Day -1 (morning dose and afternoon dose)

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
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Reference therapy, dose and mode of administration, batch number

Hyperosmotic and stimulant combined low volume bowel preparation (Sodium Picosulfate and Magnesium Citrate)

CitraFleet® Each sachet (15.08 g) contains the following active ingredients: 10.0 mg sodium picosulfate, 3.5 g magnesium oxide, 10.97 g citric acid monohydrate

Batch number: not applicable

Criteria for evaluation

Efficacy:

Primary variable:

The primary efficacy parameter was the total PDR, defined as the number of patients with at least one polyp or flat lesion as recorded by the endoscopist.

Secondary variables:

Secondary efficacy parameters were: ADR defined as the number of patients with at least one adenoma as recorded by the pathologist, number of patients with at least one flat lesion, number of patients with cancers, number of left-sided and right-sided polyps, flat lesions and poly adenomas, advanced high risk lesions, colonoscopy completion rate, quality of cleansing, acceptability and tolerability per treatment group.

Safety:

A standardised patient questionnaire assessed all AEs related to the preparation used.

Statistical methods

Sample size and expected differences: (calculations for PDR):

A difference in PDR of 14% of MOVIPREP® against CitraFleet® was assumed as a starting point.

A PDR of 44% was expected for MOVIPREP® versus 30% for CitraFleet®. This PDR detection based on studies documented in the literature (Parra-Blanco [2006], Lee [2011]) and the 14% difference on studies published by Cohen (2010) (39% vs. 20%)

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

and Matro (2010) (37% vs. 26%).

Type of analysis:
An interim analysis was conducted after data for the primary endpoint (i.e. PDR) were available for the first 400 patients included into the study.
The interim analysis indicated whether the assumptions at the beginning of the study have been adequate. The interim analysis as well as the recalculation of the sample size was performed based on an adaptive design as described by Bauer and Köhne (1994).

Power calculations:
A two-group Chi-square test with a 0.05 two-sided significance level had 80% power to detect the difference between a Group 1 proportion, p_A, of 0.440 and a Group 2 proportion, p_B, of 0.300 (odds ratio of 0.545) with a sample size in each group of 186. Assuming a drop-out rate of 7%, approximately 400 patients were required for the interim analysis with a randomisation rate of 1:1.
However, these assumptions were based on study populations described in the literature which did not exactly reflect the characteristics of the study population in this study. It was expected that the difference in the detection rates was lower due to a lower cleansing capability difference between the two preparations. Therefore, the time point of the interim analysis would have been a 'best case' scenario and would have led to termination of the study due to early success if the basic assumption for the difference in rates was true. On the other hand, the interim analysis gave the opportunity to increase the sample size within a realistic range or to stop the study due to futility.
After the interim analysis, it was decided to terminate the study as the sample size for the second part of the study would have needed to be extended by 703 patients per treatment group. That means that a total of 1806 patients should have been included in the study, exceeding the maximum number of 800 patients (400 per group) fixed in the study protocol.

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
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SUMMARY – CONCLUSIONS

Efficacy Conclusions

Within this study, the PDR following bowel cleansing with MOVIPREP® was statistically compared to CitraFleet®. No statistically significant difference in the PDR could be concluded (p-value = 0.1389) between the treatment groups. In 51.5% of all patients in whom a colonoscopy was performed and who received MOVIPREP® for bowel preparation prior to the colonoscopy, at least one polyp or flat lesion was detected. In the CitraFleet® group, the respective percentage was 44.0%.

Adenoma detection rate

For the ADR, there was a statistically significant difference between the treatment groups (p-value = 0.0409) with a higher ADR in patients who received MOVIPREP® solution (40.0%) compared to those receiving CitraFleet® (31.1%).

Polyp detection rate and adenoma detection rate by location

Regarding the location of polyps and adenomas, a statistically significant difference between MOVIPREP® and CitraFleet® was found for the detection rate of right-sided polyps and adenomas (PDR: p-value = 0.0061; ADR: p-value = 0.0251). After the bowel cleansing procedure with MOVIPREP®, patients had higher detection rates in the right half of the colon transversum, the colon ascendens and the caecum compared to CitraFleet® (PDR: MOVIPREP® = 27.5%, CitraFleet® = 16.1%; ADR: MOVIPREP® = 21.5%, CitraFleet® = 13.0%). For the detection rates of left-sided polyps and adenomas (rectum, colon sigmoideum, colon descendens and left half of colon transversum), no statistically significant difference between the cleansing solutions was found. The PDR was 38.5% for MOVIPREP® and 34.7% for CitraFleet® (p-value = 0.4363); the ADR was 19.5% for MOVIPREP® and 15.0% for CitraFleet® (p-value = 0.2411)

Detection rates of cancer, flat lesions and advanced risk lesions

Additionally, the detection rates of cancer, flat lesions and advanced risk lesions were determined. There were no statistically significant differences between the two bowel cleansing products regarding the detection rates of cancer (MOVIPREP® = 0.5%,

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
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CitraFleet® = 0.0%, p-value = 0.3253); or advanced risk lesions (MOVIPREP® = 5.5%, CitraFleet® = 4.1%, p-value = 0.5351); but a statistically significant difference was found for the detection rate of flat lesions with higher rates in the MOVIPREP® group (21.5%) compared to CitraFleet® (13.0%) (p-value = 0.0251).

Colonoscopy completion
The mean duration of the colonoscopy was similar in both treatment groups (MOVIPREP®: 19.9 min vs. CitraFleet®: 20.2 min; p-value = 0.1489) and there were only two patients in the CitraFleet® group for whom the colonoscopy had to be interrupted. During the colonoscopy, all areas of the colon were fully visible in the MOVIPREP® group but not in the CitraFleet® group. There were up to five patients without documented visualisation. The rectum was not fully visible for one patient; the colon sigmoideum, the colon descendens and the left half of the colon transversum for 2 patients; the right half of the colon transversum and the colon ascendens for 3 patients; and the caecum for 5 patients.

Quality of colon cleansing
Using the Harefield Cleansing Scale©, the colonoscopist rated the quality of colon cleansing for each single area of the colon. Generally, results in the assessment of bowel cleansing quality were better after the intake of MOVIPREP® solution than after taking CitraFleet®. In the MOVIPREP® group, the quality of downwards bowel cleansing was assessed as 'very good' (up to 56.7%) and 'good' (up to 41.8%) in most cases. 'Bad' or 'very bad' quality of bowel cleansing was either not reported or occurred in single cases only.

The quality of bowel cleansing with CitraFleet® was generally rated with much lower scores than for MOVIPREP®. For most procedures, the quality of the bowel cleansing for individual colon segments was rated either as 'good' (up to 43.0%) or 'moderate' (up to 45.1%) but for up to 30.6% as 'bad' or 'very bad' (e.g. downwards cleansing of the colon ascendens). The quality assessment 'very good' was only given up to a maximum of 13.5% with CitraFleet®.

These results are further supported when using the Harefield Cleansing Scale© to

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

evaluate the overall success of the colon cleansing procedure. In the MOVIPREP® group, 98.0% of the bowel cleansings were rated as successful and only 1.5% as failed (0.5 % were missing). In the CitraFleet® group, 57.5% of the bowel cleansings were rated as successful with 42.0% rated as failed.

Safety and Tolerability Conclusions

During the study, no deaths were reported. Overall, four patients experienced SAEs with a total of six symptoms reported. Three of these patients received MOVIPREP® and one CitraFleet®. All symptoms were assessed as being unrelated to the IMP and of mild intensity except the one in the CitraFleet® group that was of moderate intensity. One patient of the MOVIPREP® group withdrew prematurely from the study due to a 'dermatitis atopic' adverse event that was assessed as being 'probably related' to the IMP.

Overall, 100 patients (25.1%) experienced 132 TEAEs with 134 symptoms. Thereof, 93 TEAEs occurred in 66 patients (32.8%) of the MOVIPREP® group and 39 TEAEs in 34 patients (17.3%) of the CitraFleet® group. Most common symptoms were 'nausea', 'abdominal pain', 'abdominal pain upper' and 'vomiting'.

According to the assessment of the colonoscopist, 17 TEAEs were unrelated to the IMP (MOVIPREP®: 9 TEAEs [9.7%], CitraFleet®: 8 TEAEs [20.5%]). The other 115 TEAEs were assessed as having a probable or possible relationship. In the MOVIPREP® group, 55 TEAEs (59.1%) were probably related and 29 TEAEs (31.2%) possibly related; in the CitraFleet® group, 15 TEAEs (38.5%) were 'probably related' and 16 TEAEs (41.0%) were 'possibly related'. Most TEAEs (118 TEAEs [89.4%]) were assessed as being 'mild' with a comparable frequency in both treatment groups, i.e. MOVIPREP®: 83 TEAEs (89.2%), CitraFleet®: 35 TEAEs (89.7%). TEAEs of moderate intensity occurred in 9.7% of patients in the MOVIPREP® group and in 10.3% of the CitraFleet® group. The only severe TEAE occurred in the MOVIPREP® group (a case of 'herpes zoster' that was not related to the IMP).

Only small changes in vital signs and body weight were observed from V1 to V2.

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

TEAEs related to vital signs occurred in three patients of the MOVIPREP® group (unrelated hypertensive crisis, unrelated sinus tachycardia and probable related hypertension) and in one patient of the CitraFleet® group (unrelated hypertensive crisis). They were all assessed to have mild intensity.

Patients were asked to complete a questionnaire comprising four questions covering tolerance of the bowel cleansing solutions, occurrence of gastrointestinal symptoms and convenience of solution intake. Possible answers included very good, good, acceptable, bad and very bad. During the first intake, the overall tolerance of the solution was mostly 'very good' or 'good', with more patients in the CitraFleet® group than in the MOVIPREP® group who rated tolerance as 'very good' or 'good'. For the second intake, similar results were observed. However, the answer 'bad' was selected more frequently, i.e. by nine patients of the MOVIPREP® group and six patients in the CitraFleet® group. One patient of the MOVIPREP® group rated the tolerance as 'very bad'. Analogously, the overall tolerance of the two solutions was assessed.

Of those patients who were randomised into the CitraFleet® group, 96.4% had no problems at all. In the MOVIPREP® group, 63.7% of patients did not experience any problems while drinking the solution. However, 32.3% reported some problems and of these, 2.0% reported multiple problems. The most frequent symptoms were nausea and abdominal pain with higher frequencies in the MOVIPREP® group ('nausea' and 'abdominal pain': up to 16.9%) compared to the CitraFleet® group ('nausea': up to 5.6%; 'abdominal pain': up to 4.1%). Notably, 'abdominal discomfort' occurred in six patients in the MOVIPREP® group compared to three patients in the CitraFleet® group. 'Vomiting' was reported in five patients of the MOVIPREP® group and in three patients of the CitraFleet® group but only for the second dose, whereas no patient complained about 'vomiting' during the first intake.

Most patients rated the ease of drinking the solutions as 'very easy' or 'easy' with more frequent ratings of 'very easy' in the CitraFleet® group (69.0%) compared to the MOVIPREP® group (49.3%). 'Quite difficult' was only chosen by patients of the MOVIPREP® group (3.5%) and 'very difficult' by 1.0% of the MOVIPREP® and 2.5%

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

of the CitraFleet® group

Scores on a Visual Analogue Scale (VAS) showed that patients seemed to be more satisfied with the CitraFleet® intake procedure and found it also slightly more acceptable than the MOVIPREP® treatment.

Patients rated the taste of the MOVIPREP® solution after drinking the first litre with a mean value of 54.7 mm on the VAS (0 = very bad, 100 = very good) and with 49.4 mm after the second litre indicating a neutral taste. The taste of the CitraFleet® solution was rated higher, i.e. with a mean value of 77.3 mm after the first intake and 76.3 mm after the second intake of the 150 mL. These results were confirmed by the answer to the question if the taste of the bowel cleansing solution was: 'good', 'okay' or 'bad'. Most patients (59.7%) rated the taste of the MOVIPREP® solution as 'okay', 21.4% as 'good' and 17.4% as 'bad'. In the CitraFleet® group, most patients (69.5%) assessed the taste of the bowel cleansing solution as 'good', 25.4% as 'okay' and only 2.0% as bad.

DISCUSSION AND OVERALL CONCLUSIONS

The aim of this study was to compare two different bowel cleansing solutions (MOVIPREP® versus CitraFleet®) with respect to their performance measured as PDR, ADR, cancer detection rate, colonoscopy completion rate, cleansing quality as well as acceptability and tolerability. To validate whether the assumptions made at the beginning of the study were correct, an interim analysis was performed after data for the primary endpoint were available for 400 patients. Based on the results for the primary endpoint for both treatment groups, the sample size was recalculated, resulting in the conclusion that the sample size would have needed to be extended to 903 patients per treatment group. That means that in addition to the 400 patients already included into the study a further 1406 patients (i.e. 703 per treatment group) would have had to be included for the second part of the study exceeding the maximum number of 800 patients (400 per group) as stipulated by the study protocol. In consequence, the study was terminated.

Name of Sponsor/Company: Norgine Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page: N/A	*(For National Authority Use Only)*
Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

The primary endpoint, i.e. the comparison of the overall PDR, revealed a difference of 7.5% between the treatments in favour of MOVIPREP® but this difference was not statistically significant. Similar results were found for the detection rates of cancer and advanced risk lesions. However, the bowel cleansing with MOVIPREP® resulted in higher detection rates of adenomas and flat lesions compared to CitraFleet®, with better results for right-sided adenomas and right-sided polyps.

Additionally, the quality of colon cleansing was rated according to the Harefield Cleansing Scale©. In most cases, bowel cleansing with MOVIPREP® was assessed as very good and good, with very good being the rating in nearly 60% of procedures. Bad or very bad quality of bowel cleansing was either not reported or occurred in single cases only. After bowel cleansing with CitraFleet®, the quality of the procedure was generally rated with lower scores compared to MOVIPREP®. For most bowel cleansing procedures with CitraFleet®, the quality was rated as good or moderate but the assessment 'very good' was given in less than 11% of cases. These results were supported by the evaluation of the overall success of the colon cleansing procedure. According to the Harefield Cleansing Scale© in the MOVIPREP® group, bowel cleansing was rated as successful in 98.0% of cases, compared to only 57.5% of cases with CitraFleet®. From the point of view of patient acceptability, both bowel cleansing procedures were found to be acceptable and satisfactory by the majority of patients. However, patients seemed to be more satisfied with the CitraFleet® solution and also found it more acceptable than the MOVIPREP® solution. The same applied for the tolerance and the occurrence of associated symptoms. Nausea and abdominal pain were the most frequent symptoms and occurred more frequently after drinking the MOVIPREP® solution than after drinking CitraFleet®. Up to 3% of patients also complained about vomiting and abdominal discomfort but generally with lower frequency after CitraFleet® intake than after MOVIPREP®. One-third of all patients in the MOVIPREP® group experienced one or more problems, whereas only two patients experienced symptoms after drinking the CitraFleet® solution. This may be related to the larger volume of solution patients had to drink in the MOVIPREP® group. Another explanation might be the taste of the solution that was rated on average as neutral for

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Name of Finished Product: MOVIPREP®		
Name of Active Ingredient: PEG3350 (Macrogol 3350), sodium sulfate anhydrous, ascorbic acid, sodium ascorbate, sodium chloride, potassium chloride		

MOVIPREP® whereas for CitraFleet®, the taste was rated as good.

Overall, there were more AEs in the MOVIPREP® group than in the CitraFleet® group. About 90% of all TEAEs in the MOVIPREP® group were related to the study medication; in the CitraFleet® group it was almost 80%. Nearly all of these AEs were gastrointestinal symptoms including nausea, abdominal pain and vomiting. The intensity was mostly mild or moderate with one severe event (not related to IMP) in the MOVIPREP® group.

Four patients experienced SAEs, with a total of six symptoms reported overall. Three of these patients received MOVIPREP® treatment and one received CitraFleet®. All SAEs were assessed as unrelated to the IMP and were of mild intensity, except the one that occurred in the patient treated with CitraFleet® which was of moderate intensity. One patient of the MOVIPREP® group withdrew prematurely from the study due to a mild allergic dermatitis that was assessed to be probably related to the IMP.

Changes in vital sign parameters and body weight were minor in most patients. Three patients in the MOVIPREP® group and one patient in the CitraFleet® group experienced a clinically relevant abnormal cardiovascular condition of mild intensity. One of these was assessed as having a probable relation to IMP (MOVIPREP®).

In summary, the study goal of showing a difference between MOVIPREP® and CitraFleet® bowel cleansing solutions with respect to their performance, measured as PDR, ADR and other detection rates, was achieved by the detection rate of adenomas and flat lesions but not for the primary criterion, the PDR. There was a relatively high number of gastrointestinal AEs related to treatment, most being of mild intensity. This type of adverse drug reaction was expected from a bowel preparation and is mentioned in the SmPCs of MOVIPREP® and CitraFleet®.

Date of the report: 16 Dec 2013