2. SYNOPSIS

Name of Sponsor: **NORGINE Pharma**	EUDRACT Number: 2006-006873-25	
Title of the study:	A randomised, multicentre, single-blind, phase IV study of the efficacy, safety and acceptability of MOVIPREP® versus Colopeg® in colonoscopy preparation	
Coordinating Investigator:	[redacted] France	
Study Centre:	25 centres in France (23 actives)	
Studied Period:	From May 10, 2007 (first inclusion) to December 28, 2007 (last follow-up visit)	
Phase of development:	Phase IV	
Objectives:	**Primary:** To demonstrate the superiority of MOVIPREP® versus Colopeg® in gut cleansing prior to colonoscopy. **Secondary:** To assess the safety of MOVIPREP® versus Colopeg®. To assess the acceptability of MOVIPREP® versus Colopeg®.	
Phase and Design:	Multicentre, single-blind, actively-controlled, randomised, parallel group, phase IV study	
Total number of subjects (randomised and evaluable)	The sample size was chosen on the basis of previously reported studies. Taking into account all these studies a cleansing efficacy of 70% was expected for MOVIPREP® solution versus 55% for Colopeg® according to the primary efficacy endpoint. Therefore, a 15% difference between treatment groups in the proportion of patients with successful colon cleansing as judged by the blinded expert reviewer panel was considered as a clinically meaningful difference. Using a two-tailed test on the α = 5% significance level, a sample size of 360 patients (180 per treatment group) allowed a statistical power of at least 80% for the detection of a difference between treatment groups. Assuming a drop-out rate of 10%, approximately 400 patients were required to be randomised into this study with a randomisation ratio of 1:1. A total of 420 patients were screened and 419 patients were randomised in order to obtain the following populations: - *Efficacy analyses:* Intent To Treat (ITT): 400 patients (MOVIPREP® group: 202, Colopeg® group: 198) Per Protocol (PP): 359 patients (MOVIPREP® group: 178, Colopeg® group: 181) - *Safety analysis*: 400 patients (MOVIPREP® group: 202, Colopeg® group: 198)	
Inclusion criteria:	1. The patient's written informed consent had to be obtained prior to inclusion. 2. Male or female, outpatients between 18 and 85 years old with an indication to colonoscopy. 3. Willing and able to complete the entire procedure and to comply with study instructions. 4. Females of childbearing potential with an adequate method of birth control.	
Study Drugs:	MOVIPREP® (1L): PEG 3350: 100g; sodium sulphate: 7.5g; ascorbic acid: 4.7g; sodium ascorbate: 5.9 g; sodium chloride: 2,691 g ; potassium chloride: 1,015 g. Colopeg® (1L): PEG 3350: 59 g; sodium sulphate 5.682 g; sodium chloride 1.461 g; potassium chloride 0.746 g; sodium bicarbonate 1.68 g.	
Duration of treatment:	Patients receiving the 2-litre solution of MOVIPREP® began ingesting the treatment the day before the colonoscopy at 6.30 pm and drank 1 litre by 7.30 pm. From 9.00 pm to 10.00 pm, they drank the second litre. They also drank as much as they wanted, preferably at least 1 litre of additional clear liquids from 10.00 pm until midnight. Conversely, patients receiving the 4-litre solution of Colopeg® began ingesting the treatment at 5.00 pm and drank 1 litre per hour until 7.00 pm, then they took a break of 1 hour, and kept on taking the	

	2 remaining litres at the same rate, until 10.00 pm.

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Criteria for evaluation:	**Efficacy variables:** **Primary endpoint:** The proportion of patients with successful colon cleansing as judged by blinded independent expert reviewers assessing the quality of cleansing on the DVD recorded during the colonoscopy (the 3 blinded independent reviewers graded the colon cleansing only once); the final decision was based on consensus or majority (2 same assessments out of 3) on ITT population. A successful colon cleansing rate is the percentage of patients graded A (overall very good/excellent preparation) or B (overall good preparation). **Secondary endpoints:** - The proportion of patients with successful colon cleansing as judged by the colonoscopist - The colonic segment cleansing score as assessed by the colonoscopist and the blinded independent expert reviewers - The Aronchick global score (performance to clean the colon) as assessed by the blinded independent expert reviewers and the percentage of excellent to fair preparation (grade 1, 2 or 3) - The percentage of patients with at least a polyp, with at least a polyp with a diameter > 1 cm, with at least an adenoma, with at least an adenoma with a diameter > 1 cm, with at least an advanced adenoma, with at least an invasive adenocarcinoma. - Number of colonoscopies stopped because of a bad preparation - Colonoscopy to be repeated at an interval sooner than would otherwise be recommended because of poor quality of the preparation - Other examinations and their nature scheduled sooner than otherwise recommended because of imperfect quality of the preparation - Other colonoscopy examination results (assessed by experts: total duration of colonoscopy, time spent for mucosal examination during withdrawal of colonoscope) **Safety variables:** Occurrence of adverse events (AEs, SAEs and SUSARs), clinical laboratory evaluation, vital signs (blood pressure and heart rate), physical examination (including weight) and patient self-administered tolerability and acceptability questionnaire.
Statistical analysis:	**Software:** All data were analysed using the software SAS® System Windows® based version 8.2. **Descriptive statistics:** Continuous variables were described using: number of observations (N), mean (Mean), standard deviation (SD), median (Median), minimum (Min), maximum (Max) and number of missing data. Categorical and ordinal variables were presented using: frequencies (N), percentages (%) and number of missing data. **Statistical tests:** All statistical tests were two-tailed and the level of significance was set at $\alpha = 5\%$. For continuous variables, treatment groups were compared using a Student t-test. In case of a non-Gaussian variable, a non-parametric Wilcoxon-Mann-Whitney test was used. For categorical and ordinal variables, treatment groups were compared using a Chi-square test. If any expected cell frequency was less than 5 then a Fisher's exact test was used. Population analysed: overall population, 18-75; 36-49; 50-74; 75-85 years old population groups.. Further subgroups population were prospectively defined during the blind review in order to have more data in different subgroups and added to the Statistical analysis Plan: age group: 18-39, 18-49, 65-85, patients who already had a colonoscopy in the past with PEG (4L), patients who already had a colonoscopy in the past, whatever the preparation type, female, males, patients with moderate or severe renal insufficiency, mild renal insufficiency, normal renal function, patients who have a cardiovascular disease history and patients who have a GI tract disease history specially Ulcerative colitis, Crohn disease or other type of IBD.

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Summary and Conclusions

Study population:	420 patients were screened at visit V0 based on established inclusion and exclusion criteria. 419 patients were randomised but for 4 patients data were not collected because either because written informed consents were not signed on time by the patient or CRF has been lost. Thus 415 randomised patients were taken into account in the study: 210 patients in the 2-litre solution of MOVIPREP® group and 205 patients in the 4-litre solution of Colopeg® group. Fifteen patients (8 assigned to MOVIPREP® group and 7 assigned to Colopeg® group) were excluded from the ITT population (400 patients) as they did not take any amount of the investigational treatment. Protocol violations and/or investigational medications intake inferior to ¾ of the whole amount (based on the patient's questionnaire) were reported during the study for 41 patients, resulting in a PP population of 359 patients. Demographic parameters and other baseline characteristics were similar between the 2 treatment groups at inclusion (V0). Compliance based on the patient's questionnaire (at least ¾ of the whole amount of study solution drunk) was excellent for each treatment group (at least 96%).

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Efficacy results:

Table S1: Proportion of patients presenting a successful colon cleansing as judged by blinded independent experts (primary endpoint) (ITT)

Treatment groups	MOVIPREP® (N = 202)	COLOPEG® (N = 198)	Test p-value // % of difference	Total (N = 400)
Variable defining the quality of colon cleansing as judged by blinded independent experts (N and %)				
Success of colon cleansing (grade A or B)	190 (94.1%)	180 (90.9%)	0.232~ // 3.2% [-2.5; 8.8] &	370 (92.5%)
Grade A* - overall very good/excellent preparation	128 (63.4%)	130 (65.7%)		258 (64.5%)
Grade B** - overall good preparation	62 (30.7%)	50 (25.2%)		112 (28.0%)
Failure of colon cleansing (grade C or D)	12 (5.9%)	18 (9.1%)		30 (7.5%)
Grade C+ - overall bad preparation	8 (3.9%)	17 (8.6%)		25 (6.2%)
Grade D# - overall very bad preparation	4 (2.0%)	1 (0.5%)		5 (1.3%)

N=Number of patients; ITT=Intent-to-treat
** Grade A: all colon segments clean (score 3-4).*
*** Grade B: at least one colon segment with remaining small amounts of stool, fully removable or displaceable (score 2) no influence on colonoscopy results.*
+ Grade C: at least one segment with only partially removable stools (score 1) colon cannot be fully inspected.
 # Grade D: at least one colon segment, which cannot be examined related to the presence of remaining stool (score 0).
~ P-value, Pearson Chi² test (two-sided)
& 95% continuity-corrected Wald confidence interval

Three-hundred and seventy (370) out of the 400 patients from the ITT population (92.5%) presented a successful colon cleansing as judged by blinded independent experts: 190 patients (94.1%) in MOVIPREP® group and 180 patients (90.9%) in Colopeg® group.

The successful colon cleansing rate as judged by blinded independent experts was not significantly different between the 2 treatment groups (MOVIPREP® and Colopeg®) in the ITT population (p = 0.232)) with a CI of -2.5 to 8.8.

Three-hundred and forty-nine (349) out of the 400 patients from the ITT population (87.2%) presented a successful colon cleansing as judged by the colonoscopist: 177 patients (87.6%) in MOVIPREP® group and 172 patients (86.9%) in Colopeg® group.

The successful colon cleansing rate as judged by the colonoscopist was not significantly different between the 2 treatment groups (MOVIPREP® and Colopeg®) in the ITT population (p = 0.821).

On average, the cleansing scores were assessed as "good" by the blinded independent experts as well as the colonoscopist for each of the five colon segments (rectum, sigmoid, descending colon , transverse, ascending colon and caecum). Despite a trend to a better right mean colon cleansing with MOVIPREP®: 2,78 vs 2,73 for COLOPEG), there was no statistical significant difference between treatment groups MOVIPREP® and Colopeg® in the ITT population whatever the colon segment concerned (p > 0.05).

On average, the Aronchick cleansing score was assessed as "good" by the blinded independent experts with no statistical significant difference between the 2 treatment groups (MOVIPREP® and Colopeg®) in the ITT population (p = 0.897).

Three-hundred and eleven (311) patients from the ITT population (92.3%) presented an "excellent" to "fair" colon cleansing based on the Aronchick grade as assessed by the blinded independent experts: 158 patients (94.6%) in MOVIPREP® group and 153 patients (90.0%) in Colopeg® group.

The "excellent" to "fair" colon cleansing rate as assessed by the blinded independent experts was not significantly different between the 2 treatment groups MOVIPREP® and Colopeg® in the ITT population (p = 0.113).

The percentages of patients with at least a polyp, with at least a polyp with a diameter > 1 cm, with at least an adenoma, with at least an adenoma with a diameter > 1 cm, with at least an advanced adenoma, with at least an invasive adenocarcinoma (rectocolic cancer) were not significantly different between the 2 treatment groups MOVIPREP® and Colopeg® in the ITT population (p > 0.05).

No statistical significant difference was found between the 2 treatment groups MOVIPREP® and Colopeg® in the ITT population concerning the number of colonoscopy stopped because of a bad preparation, the colonoscopy to be repeated at an interval sooner than would otherwise be recommended because of a poor quality of the preparation and other examinations scheduled sooner than otherwise recommended because of imperfect quality of the preparation (p > 0.05).

No significant difference was found between treatment groups MOVIPREP® and Colopeg® in the ITT population concerning other colonoscopy examination results (p > 0.05).

Safety results:	**Adverse events** A total of 340 patients (85.0%) presented at least one AE from initiation of the investigational treatment: 162 patients (80.2%) in the MOVIPREP® group and 178 patients (89.9%) in the Colopeg® group with a significant difference between the 2 treatment groups showing a better tolerance profile in favour of the MOVIPREP® group (p = 0.007). Among these 340 patients, 330 patients (82.5%) presented at least one AE related to the investigational treatment according to the investigator's judgment: 157 patients (77.7%) in the MOVIPREP® group and 173 patients (87.4%) in the Colopeg® group with a significant difference between the 2 treatment groups in favour of the MOVIPREP® group (p = 0.011). The most frequently affected organ system from was the SOC gastrointestinal disorders (335 patients; 83.8%). Abdominal distension (233 patients; 58.3%), anal discomfort (223 patients, 55.8%), nausea (168 patients; 42.0%), abdominal pain (131 patients; 32.8%) and vomiting (39 patients; 9.8%) were the most frequent AEs from initiation of the investigational treatment. All these gastrointestinal disorders were less frequent in the MOVIPREP® group than in the Colopeg® group. AEs rated as "serious" concerned a total of 16 patients: 6 patients and 7 events before the initiation of the investigational treatment and 9 patients and 9 events from the initiation of the investigational treatment (4 SAEs in the MOVIPREP® group and 5 SAEs in the Colopeg® group). No SAE was notified by the investigator with a possible, probable or definite relation to the investigational treatment and no SUSAR was recorded. 2 SAEs led to patient's drop out - One in the Colopeg® group (large intestine perforation not related to the product) during the treatment phase - One other SAE in the Colopeg® group led (transient ischemic attack) occurred during the pre-treatment phase but was not taken into account in the safety analysis as this patient was excluded from the ITT population. No death was reported in the course of the study. **Biological Safety** Concerning biological Safety, PCSA (Potentially Clinically Significant Abnormal) values were recorded only for haematocrit levels, with no significant difference between the 2 treatment groups (5 patients (2.7%) in the MOVIPREP® group, no patient in the Colopeg® group p = 0.062). No PCSA laboratory test results led the investigators to report them as AEs. **Vital signs** Concerning the vital signs, the highest frequencies of PCSA values were recorded for diastolic blood pressure (12.4% in the MOVIPREP® group 9.6% in the Colopeg® group) and for systolic blood pressure (7.9% in the MOVIPREP® group, 7.6% in the Colopeg® group), with no significant difference between the 2 treatment groups (p > 0.05). No PCSA vital parameter values led the investigators to report them as AEs. **Physical examinations** No significant difference between the 2 treatment groups was observed with regard to physical examinations (weight and abnormalities per body system) (p > 0.05). **Tolerability and acceptability questionnaire** All the results showed a better tolerability and a better acceptability of the colonoscopy preparation in the MOVIPREP® group. **Other subgroups analysis** prospectively planned: results are reported in Appendix 14.3.5.3.

Conclusions:	**Efficacy:** No significant superiority in gut cleansing prior to colonoscopy as judged by blinded independent experts reviewers was demonstrated for MOVIPREP® over Colopeg®. Both treatments MOVIPREP® and Colopeg® were very efficient in gut cleansing as the successful colon cleansing rates were excellent (at least 90%) in both treatment groups: (94.1%) in MOVIPREP® group and (90.9%) in Colopeg® group. The findings from the primary efficacy endpoint were supported by the findings from the secondary parameters. **Safety:** The overall safety results allowed to conclude to an advantage in term of safety suggesting a better profile for the 2 litre-solution of MOVIPREP® compared to the 4-litre solution of Colopeg® in colonoscopy preparation. Moreover, statistical analysis showed that patient presented a better acceptability of MOVIPREP® in comparaison to Colopeg®.
Date of report:	October 2nd, 2008