2. SYNOPSIS

Sponsor/company **Orion Corporation** **Orion Pharma**	**Individual study table referring to a specific part of the dossier** **Volume:** **Page**	(for National Competent Authority use only)
Finished product: Pegorion®		
Active ingredient: PEG 4000		

Study code: 3066001

Study title:

Non-inferiority study; Comparison of polyethylene glycol solution with and without electrolytes for treatment of chronic constipation in elderly institutionalised patients: a double-blind, randomised, parallel-group, multicentre study.

Investigators and study centres:

The coordinating investigator was Lauri Seinelä, Tampere, Finland. The study was conducted at 10 centres (9 assisted-living facilities and 1 community nursing home) in Finland.

Development phase: IV	**Study period:** 28 Jan 2008-1 Jul 2008 (first subject first visit-last subject last visit)

Objectives:

The primary objective of the study was to show non-inferiority in efficacy of the hypotonic polyethylene glycol (PEG) product to the isotonic PEG product in elderly institutionalised patients. The other main objective was to demonstrate that hypotonic PEG is safe and well tolerated. A secondary objective was to compare the taste and willingness to use either hypotonic or isotonic PEG.

Methodology:

This was a multicentre, randomised, double-blind, parallel-group, phase IV study in a clinical in-patient setting. Institutionalised patients already consuming isotonic PEG for constipation were screened for the study. The study subjects were entered into a 1-week run-in period during which they continued their former isotonic PEG treatment for constipation. After that the study subjects were randomised into 2 parallel groups to receive either isotonic or hypotonic PEG solution for a 4-week treatment period. The randomisation into the treatment groups was stratified by dosage (once a day, twice a day or once every other day). The duration of the study was approximately 5 weeks per study subject.

Sample size:

The planned number of randomised subjects was 100, 50 per treatment group and 20-60 per study centre. As the initially planned large study centres were not able to participate in the study due to administrative reasons, recruitment was slower than planned and the study was terminated with 67 subjects. Of these, 65 study subjects started the run-in period: 31 subjects were randomised to receive hypotonic PEG and 34 subjects isotonic PEG. Number of subjects per study centre was 3-12. Number of subjects who started study treatment was 62: 30 in the hypotonic PEG and 32 in the isotonic PEG group.

Diagnosis and main criteria for inclusion:

Subjects of age 65 years or above having been institutionalised for at least 4 weeks and likely to be institutionalised for the duration of the study, written informed consent (IC) obtained, isotonic PEG treatment for constipation for at least 2 weeks at a stable dose, stool frequency at least 3 per week during the past 2 weeks.

Investigational product, dose and mode of administration, batch number:

The investigational product was Pegorion® powder for oral solution (hypotonic PEG) manufactured by Orion Corporation, Orion Pharma, Turku, Finland. The product was packed into sachets that contained 12 g of PEG each. The batch number was 1205600.

One sachet was dissolved in 200 ml of water to make a PEG solution. The hypotonic PEG solution contained 60 mg/ml PEG 4000 only. The individual dose was the same as that of the isotonic PEG product consumed by the subject during the 1-week run-in period.

Duration of treatment: The dosing of study treatments was 1-2 sachets of PEG daily or 1 sachet every other day for 4 weeks.

Reference product, dose and mode of administration, batch number:

Colonsoft® granules for oral solution (isotonic PEG) manufactured by Orion Corporation, Orion Pharma, Turku, Finland. The product was packed into sachets that contained 12 g of PEG each. The batch number was 1205297.

One sachet was dissolved in 200 ml of water to make a PEG solution. The isotonic PEG solution contained 60 mg/ml PEG 4000, 5.68 mg/ml sodium sulphate, 1.46 mg/ml sodium chloride, 0.75 mg/ml potassium chloride, and 1.68 mg/ml sodium bicarbonate. The individual dose was the same as that of the isotonic PEG product consumed by the subject during the 1-week run-in period.

Variables and methods of assessments:

Primary efficacy variable:

- Stool frequency at week 4: times/week

Secondary efficacy variables:

- Stool frequency at week 2: times/week
- Stool consistency: watery (1), soft (2), normal (3) or hard/pellet (4)
- Stool straining: no (0), slight (1) or hard (2)

Additional efficacy variable:

- The use of suppositories

Acceptability variables:

After 4-week treatment period the subjects assessed:

- Willingness to use study treatments: yes, no
- Taste: with 5-point Likert scale (very good, good, acceptable, bad, very bad)

In addition, the subjects compared the taste of isotonic and hypotonic PEG. After the last treatment dose the study subjects were given in randomised order 100 ml of isotonic PEG and 100 ml of hypotonic PEG at the time when they were to have laxative according their treatment regimen during the study. The study subjects evaluated the taste of the treatments and chose which treatment they preferred without knowing the order of the treatments.

- Taste of isotonic PEG: 5-point Likert scale (very good (1), good (2), acceptable (3), bad (4), very bad (5))
- Taste of hypotonic PEG: 5-point Likert scale (very good (1), good (2), acceptable (3), bad (4), very bad (5))
- Preference: hypotonic PEG, isotonic PEG or no difference

Tolerability assessments:

Abdominal pain, nausea, flatulence and bloating were explicitly recorded on the diary case report forms (CRFs) during the run-in and treatment periods according to the following scores: no symptoms (0), mild (1), moderate (2) or severe (3).

Safety assessments:

- Adverse events (AEs)

- Plasma electrolytes: sodium (P-Na), potassium (P-K) and magnesium (P-Mg)
- Other laboratory safety measurements: haemoglobin (B-Hb), haematocrit (B-Hcr), leucocytes (B-WBC), erythrocytes (B-Eryt) and creatinine (P-Crea)
- Vital signs: systolic and diastolic blood pressure (BP), heart rate (HR), weight and body mass index (BMI)

Statistical methods:

The primary efficacy variable:

The primary efficacy variable to show non-inferiority was the stool frequency at week 4. The primary variable was analysed using Poisson regression. The statistical model included baseline (run-in stool frequency) as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as random effects. The 2-sided 95% confidence interval (CI) for the ratio between the means of the treatments was estimated using the model specified. If the 95% CI was above the pre-specified non-inferiority margin of 0.70, hypotonic PEG was concluded at least as effective as isotonic PEG.

The secondary efficacy variables:

Stool frequency at week 2 was evaluated using the same methods as for the primary efficacy variable.

Stool consistency (watery [1], soft [2], normal [3], or hard/pellet [4]) and stool straining (no [0], slight [1], or hard [2]) at weeks 2 and 4 were other secondary efficacy variables. For stool consistency the proportion (%) of subjects with soft or normal stool consistency were calculated by treatment group. Treatment groups were compared using logistic regression. In addition the mean score of stool consistency was calculated and summarised with descriptive statistics. The mean scores for stool straining were calculated for each subject during run-in period and weeks 2 and 4. Mean scores were compared between the treatment groups using the analysis of covariance (ANCOVA). The statistical model included baseline (run-in severity score) as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as a random effect.

Additional efficacy variable:

The use of suppositories was an additional efficacy variable. The numbers of suppositories used during the treatment period and at week 4 were calculated. The Poisson regression analysis for the use of suppositories was omitted because there appeared to be no use of suppositories during week 4 and only 5 subjects on 1 occasion each during the treatment period. Therefore also the planned analysis for the primary variable with the adjustment for suppositories was omitted.

Tolerability evaluations:

Severity scores for abdominal pain, nausea, flatulence and bloating were calculated for each symptom (no symptoms (0), mild (1), moderate (2), severe (3)) as a mean score during run-in period and weeks 2 and 4. Severity scores were compared between the treatment groups using the ANCOVA methods. The statistical model included baseline (run-in severity score) as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as a random effect.

In addition, frequency for each symptom was calculated as the number of days with each symptom (mild, moderate or severe) during run-in period, week 2 and week 4. Frequencies were compared between the treatment groups using Poisson regression. The statistical model included baseline (run-in frequency) as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as a random effect.

Acceptability evaluations:

Taste, willingness and preference were analysed using nonparametric methods.

Safety evaluations:

The changes in systolic and diastolic BP, HR, weight and BMI were compared between the treatment groups using ANCOVA. The statistical model included baseline value as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as random effect.

The changes in plasma electrolytes (P-Na, P-K, and P-Mg) and other laboratory safety variables (P-Crea, B-Hb, B-Hcr, B-WBC and B-Eryt) were compared between the treatment groups using ANCOVA. The statistical

model included baseline value as a covariate, treatment, dosage and dosage*treatment interaction as fixed effects and residual error term as a random effect. In addition, the frequencies of values below, within or above the reference ranges were reported. Clinically significant deviations from the reference values were pointed out.

AEs reported or observed were classified by system organ classes (SOC) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding terminology. The number and proportion (%) of subjects having each AE were calculated by treatment group. In addition, the number of events and their proportion (%) of the total number of events were tabulated by treatment group. The number and proportion of events were additionally broken down by severity (mild, moderate, severe) and by causality (related, not related).

Evaluated data sets:

All randomised subjects who received at least 1 dose of study treatment were included in the intention to treat (ITT) data set. All study subjects with no major protocol violations were included in the per protocol (PP) data set.

Summary - Conclusions

Demography and other baseline characteristics: The mean age (range) of subjects was 85.5 (66-99) years. The majority of subjects were female (66.1%) and all subjects were Caucasian.

The proportion of subjects who were ambulatory was greater in the hypotonic PEG group (96.7%) than in the isotonic PEG group (78.1%) The mean weight was greater in the hypotonic PEG group (72.0 kg) than in the isotonic PEG group (66.8 kg). Other demographic characteristics were similar in both treatment groups.

Efficacy results:

The study met the protocol-specified primary objective, which was to show that hypotonic PEG, administered once or twice daily or every other day, is at least as good as isotonic PEG, as determined by a non-inferiority analysis of stool frequency at week 4. The mean stool frequency ratio (95% CI) of hypotonic PEG and isotonic PEG was 0.90 (0.74-1.10) at week 4 in the PP population. As the 95% CI of the ratio between the hypotonic and isotonic PEG treatments was within the 30% margin (i.e. the lower CI limit was above 0.70) that was predefined as the criterion for the demonstration of non-inferiority, hypotonic PEG was concluded to be non-inferior to isotonic PEG. The results in the PP population at week 2 and in the ITT population at weeks 2 and 4 supported the result of the primary analysis.

The proportion of subjects with soft or normal stool consistency was numerically greater in the hypotonic PEG group than in the isotonic PEG group in both the PP and ITT populations. However the only statistically significant difference between the groups was detected in the ITT population at week 2: the proportion of subjects reporting soft or normal stools was 62.1% in the hypotonic PEG group compared with 37.5% in the isotonic PEG group ($p = 0.045$) in the ITT population. The mean scores for stool consistency were between 2 (soft) and 3 (normal) throughout the study in both groups.

The mean scores for stool straining remained relatively unchanged in both treatment groups throughout the study both in the PP and ITT populations. The mean scores for stool straining were between 0 (no) and 1 (slight) in both groups, with no statistically significant between-group differences detected.

Only few subjects (n = 5) needed suppositories on 1 occasion during the treatment period.

The proportion of subjects that was willing to use study treatment or rated the taste of the study treatment good or acceptable was numerically, but not statistically, greater in the hypotonic PEG group than in the isotonic PEG group. The majority of subjects in both groups were willing to use study treatment; 85.2% of subjects in the hypotonic PEG group and 63.0% in the isotonic PEG group ($p = 0.070$) in the PP population. The majority of subjects also rated the taste of PEG product good or acceptable, with 88.5% of subjects in the hypotonic PEG group and 69.2% in the isotonic PEG group ($p = 0.101$) in the PP population.

After tasting both PEG products in random order at the end of the study, isotonic PEG was more often rated good than hypotonic PEG (42.4% vs 19.0%) but also more often bad than hypotonic PEG (16.9% vs. 10.3%) in the ITT population. The mean scores of the taste, as assessed with the 5-point Likert scale, were similar in both groups; the mean score (SD) was 2.9 (0.5) for hypotonic PEG and 2.7 (0.7) for isotonic PEG. No

statistically significant differences between the groups were detected in the preference of PEG product, with 36.8% of subjects preferring hypotonic PEG, 45.6% isotonic PEG and 17.5% having no preference.

Safety results: The overall incidence of AEs was low in both treatment groups: 9 events in the hypotonic PEG group and 13 in the isotonic PEG group. The most common AE was urinary track infection (in 3 subjects in the hypotonic PEG group). All AEs were mild or moderate in severity and none was considered to be related to study treatment. All SAEs were hospitalisations, including 4 events (in 3 subjects) during the study treatment, 1 during the run-in and 1 before the run-in period. Only 1 subject discontinued the study treatment due to AEs.

A statistically significant difference in plasma sodium was observed between the treatment groups at week 4. However, the mean changes from baseline to week 4 (decrease of 138.8 to 137.7 mmol/l in the hypotonic PEG group and increase from 138.6 to 138.9 mmol/l in the isotonic PEG group) were not considered to be clinically significant. In addition, there were no clinically significant abnormalities in plasma sodium in any subject or interventions in any subject due to change in plasma sodium. No other differences between the treatment groups were detected in any other electrolyte or other laboratory safety variables.

No clinically or statistically significant differences between the treatment groups were detected in diastolic or systolic BP, HR, weight or BMI.

Tolerability results:

For abdominal pain, nausea, flatulence and bloating, the mean severity scores and numbers of events were low in both treatment groups throughout the study. No statistically significant differences between the treatment groups were detected in any of these variables.

Conclusion: In elderly institutionalised patients, the hypotonic PEG product (Pegorion®) is non-inferior to the isotonic PEG product (Colonsoft®) in efficacy. Both PEG products are safe, well tolerated and, when dissolved in water, well accepted by the patients.

Date of report: 31 Oct 2008