Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	19 JUN 2012
Study title:	A Randomized, Open-Label, Dose-Finding Trial of Polyethylene Glycol 3350 Laxative Plus Electrolytes for the Treatment of Constipation
Sponsor's study number:	18129
NCT number:	NCT01212445
EudraCT number:	2010-021367-32
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	The primary objective of the study was to evaluate the proportion of subjects with a bowel movement (BM) without straining or without hard and/or lumpy stool within the first 24 h of treatment for subjects taking 1 of 3 single doses of polyethylene glycol (PEG) plus electrolytes (PEG+E) (13.125 g, 26.25 g, 39.375 g). The doses specified relate to the doses of PEG. Secondary objectives were measured by analysis of a subject diary and self-reported BM data. The secondary objectives included comparisons of PEG+E doses at 24 h for: BM control; relief of gas; relief of bloating; and relief of abdominal discomfort/cramping. In addition, the proportion of subjects with a BM (without straining and without hard and/or lumpy stool) within the first 24 h of treatment for subjects taking different doses of PEG+E was evaluated for the time to first BM.
Test drug:	Polyethylene glycol/macrogol + electrolytes (Movicol®, BAY 81-8430)
Name of active ingredient(s):	PEG/macrogol + E (sodium chloride, sodium hydrogen carbonate, and potassium chloride)
Dose:	PEG: 13.125 g (1 x 1 sachet), 26.25 g (2 x 1 sachet), or 39.375 g (3 x 1 sachet) of PEG, dissolved in 125, 250, or 375 mL of non-carbonated water, respectively E: Sodium chloride 350.8 mg, sodium hydrogen carbonate 178.6 mg, and potassium chloride 50.2 mg
Route of administration:	Oral
Duration of treatment:	1 day
Reference drug:	Not applicable
Indication:	Constipation
Diagnosis and main criteria for inclusion:	• Male or female subjects aged 18 years or older who met two or more of the following modified Rome III-based criteria for constipation: (a) straining during at least 25% of defecations; (b) lumpy or hard

stools in at least 25% of defecations; (c) sensation of incomplete evacuation for at least 25% of defecation; (d) sensation of anorectal obstruction/blockage for at least 25% of defecations; (e) manual maneuvers to facilitate at least 25% of defecations (eg, digital evacuation, support of the pelvic floor), and (f) fewer than 3 defecations per week

- Must be ambulatory
- Criteria fulfilled for the last 3 months with symptom onset at least 6 mo prior to diagnosis
- Had a self-reported or documented history of chronic constipation
- Agreed not to use laxatives other than the study treatment from the baseline/informed consent to the end-of-study
- Agreed to maintain a similar diet from the week before Visit 3 to the end-of-study
- Additionally required not to use any treatment known to cause constipation during the study (for subjects enrolled after Amendment 1)
- If a female subject, either surgically sterile, 2 years postmenopausal, or using an acceptable method of contraception. Abstinence was not an acceptable method of contraception. Females of childbearing potential had to have a urine pregnancy test (human chorionic gonadotropin [HCG]) that was negative at Visit 3
- Be able to read and write in the diaries in English

Study design: The study was conducted in a single-center, open-label, randomized design.

Methodology: Each subject received a single oral dose of PEG+E containing either 13.125 g, 26.25 g, or 39.375 g of PEG. There were 4 study visits: a pre-screening interview via telephone (Visit 1); informed consent and a baseline evaluation (Visit 2); randomization if a subject qualified for a 1 day open-label treatment period (Visit 3); and an end-of-study visit (Visit 4). Subjects completed a study diary following treatment by recording the time and an evaluation of each BM for the next 24 h. Subjects either returned to the study site for Visit 4 after 1-2 days, or returned the diary by post.

Using the Bristol stool scale as a reference, subjects indicated whether the BM was accompanied by straining (yes or no and Visual Analogue Scale [VAS]) and whether the stool was hard or lumpy (yes or no and VAS). In addition, they used a VAS to assess:

- Control (calm [not urgent] to not able to hold [very urgent])
- Gas (none to severe)
- Bloating (none to severe)

- Cramping (none to painful)

At Visit 4, the subjects were asked to rate their global assessment of the study treatment according to the categories below:

- 0 = not at all effective
- 1 = a little bit effective
- 2 = moderately effective
- 3 = quite a bit effective
- 4 = extremely effective

The duration of the study was between 6 and 16 days, which allowed for pre-study screening, administration of a single dose of PEG+E per subject, and evaluation of efficacy and adverse events (AEs).

Safety and tolerability of PEG + E were monitored throughout the study.

Study center(s): The study was conducted at a single center in Ireland.

Publication(s) based on the study (references): None at the time of report creation.

Study period: **Study Start Date:** 01 OCT 2010

Study Completion Date: 23 NOV 2011

Early termination: Not applicable

Number of subjects: **Planned:** 175 subjects

Analyzed: 154 subjects

Criteria for evaluation

Efficacy: 24 h documentation of BM control, gas, bloating, and abdominal discomfort/cramping using a subject diary and subject's global assessment of treatment

Primary efficacy endpoint:

- Proportion of subjects with successful BM (ie, BM with no straining or hard/lumpy stools) within 24 h of dosing

Secondary efficacy endpoints:

- Proportion of subjects with successful BM within 12 h of dosing
- Time to first successful BM
- VAS ratings for BM control
- VAS ratings for gas
- VAS ratings for bloating
- VAS ratings for abdominal discomfort/cramping

	• Subject's global assessment of treatment ***Safety:*** AEs and the use of concomitant medication were evaluated.
Statistical methods:	AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were classified by system organ classes and preferred terms. The general strategy of the safety evaluation was to examine the summaries for any trends. No formal hypothesis testing was carried out. All hypothesis tests were 2-sided and performed using a 5% significance level. There was no formal hypothesis testing of baseline data. The proportion of subjects with a successful BM within 24 h of dosing was calculated for each dose group along with 95% confidence intervals (CIs) based on exact binomial statistics. The rates were compared between each pair of treatments using an exact 2-sided test (Fisher's). In addition, a logistic regression analysis was performed with successful BM as the dichotomous dependent variable and dose as the independent variable. Kaplan-Meier summary statistics and number of events (ie, subjects with a successful BM without straining and hard and/or lumpy stool) and censored values were presented by dose group for time to first successful BM. A log rank test was used for pairwise comparisons of each of the dose groups. The proportion of subjects with a successful BM within 12 h of dosing was analyzed and presented similarly to the primary efficacy analysis. The VAS ratings were averaged to yield a single score for each VAS endpoint for each subject. Subjects who reported no BMs were omitted from this analysis. Descriptive statistics were presented for each averaged VAS endpoint by dose group. Each of the averaged VAS endpoints was compared between dose groups using an analysis of covariance (ANCOVA), with the number of stools per week (from the Constipation Assessment at Visit 2) used as a covariate. Differences in the adjusted means, 95% CI for the differences in adjusted means, and corresponding p-values were presented. The subject's global assessment of treatment recorded at Visit 4 was analyzed using a similar ANCOVA to the VAS ratings analysis, including dose group and the number of stools per week as covariates in the model.
Substantial protocol changes:	Amendment 1 from date 21 OCT 2010 introduced the following changes: • Following the guideline for the Modified Rome III constipation criteria, a change was made to move the frequency of the BM from a must inclusion criterion to one of the required criteria for diagnosis of constipation. Additionally the straining frequency was also updated based on the Modified Rome III constipation criteria. Two or more of the listed symptoms were now necessary for satisfying Rome III criteria-based diagnosis of constipation. • A decision had been made to evaluate the efficacy of study treatment in subjects on constipation-causing medications. Consequently, the list of allowed medications was amended to include such medications.

- The time gap between Visit 2 and Visit 3 was increased from 2 to 3 days to 2 to 7 days.
- A typo was corrected in an inclusion criterion to clarify that informed consent form (ICF) was signed on Visit 2 not Visit 1.

Subject disposition and baseline

A total of 154 subjects were randomized to receive a single treatment of PEG+E at 1 of 3 doses: 52 subjects were randomized to the 13.125 g PEG+E dose group and received 13.125 g of PEG, 51 subjects were randomized to the 26.25 g PEG+E dose group and received 26.25 g of PEG, and 51 subjects were randomized to the 39.375 g PEG+E dose group and received 39.375 g of PEG. All 154 subjects received the single treatment of PEG+E at the dose level to which they were randomized and completed the study; no subject was withdrawn from the study for any reason. All enrolled subjects in each dose group were included in the intent-to-treat (ITT), completed subjects (CS), and safety populations.

Of the 154 subjects enrolled in the study, 86.4% were female, with a similar high percentage in each of the dose groups. More male subjects were randomized to the 39.375 g PEG+E dose group than the other 2 dose groups. Overall, subjects were between 18 and 84 years of age, and the mean age was 46.5 years. Mean age, height, weight, and BMI were similar for all dose groups. The BMI values ranged between 14.42 and 64.10 kg/m^2 and mean BMI was 25.795 kg/m^2.

All pregnancy tests were negative or not applicable/not done.

The median (range) duration of constipation was 5.7 (0-56) years, 4.7 (0-44) years, and 5.8 (0-31) years for the 13.125 g, 26.25 g, and 39.375 g PEG+E dose groups, respectively. The median number of stools (2.0) per week was the same for each dose group. The number of subjects who answered yes or no to the other questions about their disease was similar for each of the dose groups.

Seven subjects in each of the 13.125 g and 26.25 g PEG+E dose groups and 5 subjects in the 39.375 g dose group were taking at least 1 medication or herbal remedy before the start of the study.

Efficacy evaluation

All subjects entered into the study were included in both the ITT and CS populations; therefore the results are only presented for the ITT population.

Ten (19.2%), 16 (31.4%), and 10 (19.6%) subjects in the 13.125 g, 26.25 g, and 39.375 g PEG+E dose groups, respectively, had a successful BM within 24 h of dosing. Using a Fisher's Exact Test, no statistically significant differences in the proportion of subjects who had a successful BM within 24 h of dosing were observed in all pairwise comparisons between the 3 dose groups. These conclusions were supported by the robustness analysis using a Logistic Regression model.

The proportion of subjects who had a successful BM within 12 h of dosing was 4 (7.7%), 8 (15.7%), and 6 (11.8%) subjects in the 13.125 g, 26.25 g, and 39.375 g PEG+E dose groups, respectively.

The time to the first successful BM ranged between 0.0 and 2.5 days for subjects in the 13.125 g PEG+E dose group and between 0.1 and 2.6 days for subjects in the 26.25 g and 39.375 g PEG+E dose groups, respectively.

No statistically significant difference in the proportion of subjects who had a successful BM within 12 h of dosing or in the time to first successful BM was observed in pairwise comparisons between the 3 dose groups.

A statistically significant difference in the average VAS rating for bloating was observed in a pairwise comparison between the 13.125 g and 26.25 g PEG+E dose groups (p=0.048), where a lower rating, indicating less severe bloating, was observed for the higher of the 2 dose groups. No statistically significant difference in the average VAS rating for bloating was observed in the pairwise comparisons between 13.125 g and 39.375 g dose groups and 26.25 g and 39.375 g PEG+E dose groups. In addition, no statistically significant difference in the average VAS ratings for BM control, gas, and abdominal discomfort/cramping was observed in the pairwise comparisons between the 3 dose groups.

The median subject's global assessment of treatment score was 1.0, a little bit effective (range 0 [not at all effective] to 4 [extremely effective]) for all dose groups. No statistical difference in the subject's global assessment of treatment score was observed in the pairwise comparisons between the 3 dose groups.

Safety evaluation

During the study, a total of 7 (4.5%) subjects reported 8 treatment-emergent AEs (TEAEs). A similar number of subjects in each dose group reported TEAEs during the study: 3 (5.8%) subjects in the 13.125 g PEG+E dose group and 2 (3.9%) subjects in each of the 26.25 g and 39.375 g PEG+E dose groups. All but one of the TEAEs was treatment-related. Treatment-related TEAEs were reported for 3 (5.8%), 1 (2.0%), and 2 (3.9%) subjects in the 13.125 g, 26.25 g, and 39.375 g PEG+E dose groups, respectively.

The most frequently reported system organ class was gastrointestinal (GI) disorders, reported for a total of 3 subjects: 2 subjects in the 13.125 g PEG+E dose group (TEAEs of abdominal pain lower and nausea) and 1 subject in the 39.375 g PEG+E dose group (TEAEs of abdominal pain and abdominal distension). TEAEs of headache were reported for 2 subjects: 1 subject in each of the 26.25 g and 39.375 g PEG+E dose groups. The other TEAEs were each reported for 1 subject (TEAEs of eye pruritus and cough).

No severe AEs were reported during the study. Three TEAEs (nausea, abdominal distension, and abdominal pain) were considered to be moderate in severity. All other TEAEs were mild in severity. No serious AEs (SAEs) or TEAEs leading to withdrawal or death were reported during the study.

Thirty-eight, 37, and 35 subjects in the 13.125 g, 26.25 g, and 39.375 g dose groups, respectively, took at least 1 concomitant medication or herbal remedy during the study. The most commonly taken concomitant medications were: glucosamine, omeprazole, rosuvastatin, and calcichew D3 Forte (calcium carbonate and colecalciferol), each taken by a total of 6 subjects across dose groups. The proportion of subjects taking a concomitant medication or herbal remedy was similar between the dose groups.

Forty, 41, and 35 subjects in the 13.125 g, 26.25 g, and 39.375 g dose groups, respectively, had any previous laxative use. The most frequently used previous laxative was senokot (sennosides) followed by dulcolax (bisacodyl). The proportion of the subjects who had previously used any laxative was similar between the dose groups.

Overall conclusions

- In this study, the proportion of subjects who had a successful BM within the first 24 h was ≤31.4% of subjects in any dose group after dosing with 1 of 3 doses of PEG+E (containing 13.125 g, 26.25 g, or 39.375 g of PEG).
- No statistically significant difference in the proportion of subjects with a successful BM within the first 24 h after dosing was observed between the 3 dose groups.
- Similarly, no statistically significant difference in the proportion of subjects achieving successful BM within 12 h of dosing was observed between the 3 dose groups.
- In general, no statistically significant differences in the average VAS ratings for BM control, gas, bloating, and abdominal discomfort/cramping were observed between the 3 dose groups.
- No statistically significant difference in the time to first successful BM was observed between the 3 dose groups.
- PEG+E at all 3 doses was considered to be safe and well tolerated.