SYNOPSIS

Name of Sponsor/Company	Xian Janssen Pharmaceutical Ltd
Name of Investigational Product	JNJ-437580-AEO (Prucalopride)

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Prepared by: Xian Janssen Pharmaceutical Ltd

Protocol No.: PRUCOP4005

Title of Study: A Multicenter, Single-Arm, Interventional, Phase 4 Study to Evaluate the Efficacy and Safety of Prucalopride in Combination With PEG or Lactulose in Women With Chronic Constipation (CC)

NCT No.: NCT02228616

Clinical Registry No.: CR102381

Coordinating Investigator: Sanren Lin, MD, [redacted] Third Hospital, [redacted] China.

Study Center(s): This study was conducted at 16 sites in China.

Publication (Reference): None

Study Period: 15 October 2014 to 28 September 2016, Database lock date was 25 November 2016

Phase of Development: 4

Objectives:

Primary Objective

The primary objective of this study was to evaluate the efficacy of prucalopride 2-mg, given orally once daily for 12 weeks, in combination with polyethylene glycol (PEG) or lactulose, in treatment of women with chronic constipation (CC) in whom laxatives failed to provide adequate relief, as measured by the percentage of subjects with a weekly average increase of ≥1 spontaneous complete bowel movements (SCBMs) (responders) during the 12-week Treatment Phase fas compared to the baseline.

Secondary Objectives

Efficacy

- Percentage of subjects with a weekly average 3 or more SCBMs during the 12-week Treatment Phase as compared to the baseline.
- Percentage of subjects with a weekly average increase of ≥1 SCBMs during the first 4-week Treatment Phase as compared to the baseline.
- Percentage of subjects with a weekly average increase of ≥1 spontaneous bowel movements (SBMs), bowel movements (BMs) during the 12-week Treatment Phase as compared to the baseline.
- Average number of SCBMs per week.
- Average number of SBMs per week.
- Average number of all BMs per week.

- Percentage of BMs with normal consistency (Types 3 to 4 based on Bristol Stool Scale) per week.
- Average weekly change of PEG or lactulose frequency and dosage as compared to baseline during the 12-week Treatment Phase.
- Improvement of constipation symptoms and higher satisfaction levels as measured by Patient Assessment of Constipation-Symptom Questionnaire (PAC-SYM) scores.
- Improvement in physical, psychological, and emotional stress as measured by Patient Assessment of Constipation-Quality of Life Questionnaires (PAC-QOL) scores.

Safety

- To evaluate the overall safety of the 2-mg dose of prucalopride in subjects with CC as measured by adverse events (AEs).

Methodology:

This was a multicenter, open-label single-arm, interventional study to evaluate the efficacy and safety of prucalopride in treatment of women with CC in real clinical practice.

It consisted of 2 phases: a 1-week Run-in Phase and a 12-week open-label Treatment Phase. Study population was women with CC who had been treated with laxatives but failed to obtain adequate relief within the preceding 6 months. Subjects who met the inclusion criteria and did not meet the exclusion criteria were enrolled in the study and signed an informed consent form (ICF). They were instructed not to change their diet, lifestyle during the study.

During the first week of the study (Run-in Phase), subjects continued PEG or lactulose treatment, and they were not allowed to use any other laxatives and drugs for CC. Subjects were required to maintain a written stool diary as well as the use of PEG and lactulose.

Following the Run-in Phase, subjects entered the 12-week open-label Treatment Phase. During the Treatment Phase, subjects were treated for 12 weeks with prucalopride 2-mg, given orally once daily with or without breakfast in the morning. Subjects were required to continue PEG or lactulose treatment with the same dosage as that in the Run-in period. If necessary, due to intolerable side-effects (ie, severe diarrhea), dosage decrements of PEG or lactulose treatment were made at any time or the subject could discontinue the PEG or lactulose treatment, based on investigator's judgment. If investigators added back laxatives in later stage, the dosage was not to be greater than that at baseline. Subjects recorded study drug and laxative medication dosing information and information related to BMs in a daily diary throughout the study. The PAC-SYM and PAC-QOL questionnaires were completed at Weeks 0, 4, and 12. Subject safety was monitored throughout the study. Details on the timing of the treatment and assessments are given in the Time and Events Schedule located in the protocol.

Drugs affecting the colonic motility (ie, anticholinergics [not including antihistamines], opioids, spasmolytics, prokinetics, and tricyclic antidepressants) were prohibited during the study.

End-of-treatment /early withdrawn assessments were obtained if a subject discontinued study treatment before the end of the Treatment Phase.

Number of Subjects (planned and analyzed):

Planned: The plan was to enroll 280 subjects in this study.

Analyzed: A total of 278 subjects received at least 1 dose of the study drug and were included in the evaluable analysis set.

Diagnosis and Main Criteria for Inclusion:

Women aged 18-65 years, inclusive, with CC in whom laxatives failed to provide adequate relief within the preceding 6 months and who had been using PEG or lactulose treatment for more than 1 week at screening were enrolled in the study. For screening phase, the subjects were required to have reported a weekly average of ≤2 SBMs and ≥1 of the following within the preceding 3 months before the screening visit, while symptom onset was more than 6 months before the screening visit:

- Very hard (little balls) and/or hard stools in more than 25% of BMs;
- Sensation of incomplete evacuation in more than 25% of BMs;
- Straining at defecation in more than 25% of BMs;
- Sensation of a no-rectal obstruction or blockade in more than 25% of BMs;
- Need digital manipulation to facilitate evacuation in more than 25% of BMs.

For Treatment Phase, the subjects were required to have ≤2 SCBMs during the 1-week Run-in Phase

Test Product, Dose and Mode of Administration, Batch No.:

During the first week of the study (Run-in Phase), after investigator optimized the PEG or lactulose treatment, the subjects had to maintain the therapy. (According to PEG and lactulose local label, the recommended dosage and administration was: PEG 4000, 10 g, once daily-twice daily (QD-BID); Lactulose 10-25 mL/d).

During the Treatment Phase subjects continued PEG or lactulose treatment with the same dosage as that in the Run-in Phase. In case of diarrhea, dosage decrements of PEG or lactulose treatment were allowed based on investigator's judgment and the subject could discontinue the PEG or lactulose treatment. If investigators added back laxatives in later stage, the dosage was not to be greater than that at baseline.

Prucalopride (4 batches: EEL5S00; EIL3R02; EKL2900; DCL7E00) was administered orally at the daily dose of 1 tablet of 2-mg with or without breakfast in the morning during 12-week Treatment Phase.

Reference Therapy, Dose and Mode of Administration, Batch No.:

There was no reference therapy in this study.

Duration of Treatment:

The total study duration was of 13 weeks including 6 visits to the study site. There was a 1-week Run-in Phase followed by a 12-week Treatment Phase.

Criteria for Evaluation:

Efficacy Evaluations

The subjects maintained a daily diary for the entire duration of the study to record the date, time and dosage of study drug and laxatives, and the information about their BM. The subjects completed the PAC-SYM questionnaire and PAC-QOL questionnaire at the time points specified in the Time and Events Schedule located in the study protocol, before any assessments were carried out. The subjects recorded the severity of her symptoms and quality of life occurring during the 2 weeks preceding the visit.

Primary Endpoint

The primary efficacy endpoint was the percentage of subjects with a weekly average increase of ≥1 SCBMs during the 12-week Treatment Phase as compared to the baseline.

Secondary Endpoints

- Percentage of subjects with a weekly average 3 or more SCBMs during the 12-week Treatment Phase as compared to the baseline.
- Percentage of subjects with a weekly average increase of ≥1 SCBMs during the first 4 weeks of the Treatment Phase as compared to the baseline.
- Percentage of subjects with a weekly average increase of ≥1 SBMs, BMs during the 12-week Treatment Phase as compared to the baseline.
- Average number of SCBMs per week.
- Average number of SBMs per week.
- Average number of all BMs per week.
- Percentage of BMs with normal consistency (Types 3 to 4 based on Bristol Stool Scale) per week.
- Average weekly change of PEG or lactulose frequency and dosage as compared to baseline during the 12-week Treatment Phase.
- Improvement of constipation symptoms and higher satisfaction as measured by PAC-SYM scores. Improvement was defined as that the mean score reduction from baseline of ≥0.2.
- Improvement in physical, psychological, and emotional stress as measured by PAC-QOL scores. Improvement was defined as that the mean score reduction from baseline of ≥0.3.

Safety Evaluations

Safety was evaluated by monitoring AEs, vital signs, physical examinations, and 12-lead electrocardiograms (ECG). Hematology/chemistry/urinalysis tests were to be performed only in subjects in whom investigators needed to further define her eligibility after medical history and physical examination within 2 weeks before screening and at end of treatment (EOT) / early withdraw visit. Pregnancy test was to be performed in women with childbearing potential to exclude pregnant women at screening visit and EOT/early withdraw visit.

Statistical Methods:

Analysis Sets: Evaluable Analysis Set and Per Protocol (PP) analysis set were used to present information.

Evaluable Analysis Set included all subjects who received at least one dose of study treatment. It was the primary analysis set for all demographic, efficacy and safety data analyses.

The PP Analysis Set included all subjects in Evaluable analysis set with no major protocol deviations. Subjects with only partial deviations were considered part of the PP analysis set but their data were excluded from the date of their deviation onwards.

Sample Size Determination: In previously conducted study PRUCRC3001 the percentage of subjects with a weekly average increase of ≥1 SCBMs (response rate) during the 12-week Treatment Phase in the Phase 3 trial was 57.2%. However, the response rate was expected to be lower in this Phase 4 study. A sample size of 195 subjects in the prucalopride group was determined based on at least 80% power that would provide a 95% confidence interval (CI) of the point estimate with the lower limit response rate of 35% assuming the overall response rate of 45%. With dropout rate considered as 30%, the plan was to recruit 280 subjects into the study.

Primary Efficacy Analysis: The primary endpoint was the percentage of subjects with a weekly average increase of ≥1 SCBMs during the 12-week Treatment Phase as compared to the baseline. The SCBMs per week of the whole Treatment Phase were analyzed by descriptive statistics with their frequency; the percentage and 95% CI were estimated. In addition, comparison between responder rates [observed % minus 35% (expected)] was performed using the normal approximation method, and the responder rate of the 12-week treatment was to be concluded to be greater than 35% when a 2-sided p value of less than 0.05 was observed.

Secondary Efficacy Analyses: Descriptive statistics similar to primary endpoint were applied for the analysis of dairy card related assessments. The raw and change from baseline in total PAC-SYM and PAC-QOL score and each subscale score at Week 4 and Week 12 were summarized with descriptive statistics along with the p value from 2-sided paired t-test on change from baseline. The proportion of subjects that have a response of 'Improved' in total score and each subscale score at Week 4 and Week 12 were summarized with an estimated 2-sided 95% CI using the normal approximation to binomial distribution.

Safety Analyses: Safety evaluable subjects included all subjects who received at least one dose of study treatment. The TEAEs were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. Safety was evaluated by examining the incidence and types of AEs, physical examination and vital signs from the screening phase through study completion. Descriptive statistics were calculated for each clinical laboratory parameter and vital sign measurements at baseline and at each scheduled time point. Any post baseline shifts in physical examination findings compared to baseline were summarized and any abnormal or clinically meaningful changes from baseline in ECG findings were reported as AEs.

RESULTS:

STUDY POPULATION:

Of the 278 subjects who were enrolled and received at least 1 dose of study drug, 246 subjects completed the study treatment. Thirty-two subjects discontinued the study and reasons for discontinuation were: AE (11), protocol violation (6), withdrawal by subject (6), lack of efficacy (4), lost to follow-up (2), other (2), and pregnancy (1).

All subjects were females of Asian origin who had median age of 44.0 years (range 18 to 66 years) and median body mass index (BMI) was 21.72 kg/m^2 (range 14.98 to 33.33 kg/m^2).

The duration of constipation was ≥1 year for almost all subjects (98.9%); 76.5% of subjects had a duration of constipation ≥ 5 years.

EFFICACY RESULTS:

All efficacy analysis were performed on the evaluable analysis set population, which included all subjects who received at least 1 dose of study drug. For sensitivity purpose, primary efficacy analysis was also performed on the PP population.

Primary efficacy analysis

- During the Treatment Phase, in the evaluable analysis set, 74.1% of subjects reported an average increase of at least 1 SCBM/week. The percentage of responders during Treatment Phase was 39.1% higher than the predefined expected responder rate of 35%.
- The results of PP population were in line with the results reported for evaluable analysis set population. In the PP population, 80.2% of subjects reported an average increase of at least 1 SCBM/week. The percentage of responders during Treatment Phase was 45.2% higher than the predefined expected responder rate of 35%.

Secondary efficacy analysis

- More than half of the subjects with valid diary entries (55.4%) reported ≥3 SCBMs/week.
- Among 264 subjects with valid diary entries, 192 (72.7%) subjects reported an average increase of ≥1 SCBMs per week during Weeks 1-4.
- An average increase of at least 1 SCBM, SBM, and BM per week was reported during Weeks 1 to 12, each 4-week interval (Weeks 1-4, 5-8, and 9-12), and each of the first 4 weeks of Treatment Phase. The percentage of subjects with average increase of ≥1 SBMs and BM per week increased from 83.2% at Week 1 to 88.8% and 87.6%, respectively at Week 4 and was 88.0% and 86.7%, respectively across the entire 12-week Treatment Phase. Similar increase was also reported for the average increase of ≥1 SCBMs per week, during the entire Treatment Phase.
- In comparison to the baseline values, there was a significant increase ($p<0.001$) in the average number of SCBMs per week during Weeks 1 to 12, each 4-week interval (Weeks 1-4, 5-8, and 9-12), and each of the first 4 weeks of Treatment Phase. As early as Week 1 of prucalopride 2-mg treatment, the mean of average number of SCBMs per week increased to 3.17 from 0.36 as reported during Run-in Phase (baseline). The effectiveness of prucalopride 2-mg in improving constipation was sustained over the 12-week Treatment Phase, with mean of average number of SCBMs per week 3.67 across the entire 12-week treatment period.
- During the course of prucalopride treatment (Weeks 1 to 12), majority of the subjects (96.8%) reported BMs with normal consistency which improved from baseline condition when less than half of the subjects (47.1%) had normal BMs.
- During the 12-week Treatment Phase, subjects used osmotic laxatives less frequently. Statistically significant mean (SD) decrease of 1.99 (3.369) and 3.56 (4.808) was reported for per week frequency of PEG and lactulose during the Treatment Phase ($p <0.001$). The mean (SD) percentage change from baseline for average weekly frequency of PEG and lactulose was statistically significant, 26.11 (37.594)% and 37.69 (48.623)% respectively.
- Statistically significant reduction in total scores and subscale scores at Week 4 and Week 12 was recorded by subjects for PAC-SYM questionnaires. At the end of study treatment (Week 12), 84.6% subjects reported improvement of ≥0.2 points in overall PAC-SYM scores.
- Statistically significant reduction in total scores and subscale scores at Week 4 and Week 12 was also recorded by subjects for PAC-QOL questionnaires. At the end of study treatment (Week 12), approximately 86.3% subjects reported improvement of ≥0.3 points in overall PAC-QOL scores.

SAFETY RESULTS:

An overview of TEAEs is presented in the below table.

Overview of Treatment-Emergent Adverse Events (Evaluable Subjects)

Analysis Set: Evaluable Safety Outcome	PRU 2 mg (N = 278) n (%)
Any TEAE	97 (34.9)
Any severe TEAE	7 (2.5)
Any study drug related TEAE	71 (25.5)
Any laxative related TEAE	23 (8.3)
Any TEAE leading to study withdrawal	11 (4.0)
Any serious TEAE	1 (0.4)
Deaths	0

Note: Percentages calculated with the number of subjects in PRU group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events
Study drug related adverse events included adverse events with causality to study drug judged as possible, probable and very likely or events with missing causality.
Laxative related adverse events included adverse events with causality to laxative judged as possible, probable and very likely.

The most frequently reported TEAEs reported in at least 2% of the subjects is mentioned in table below. The most frequently reported TEAE was headache (33 [11.9%] subjects) followed by dizziness (22 [7.9%] subjects), diarrhea and nausea (each reported in 14 [5%] subjects).

Treatment-Emergent Adverse Events in at Least 2% of Subjects in Prucalopride Group by System Organ Class and Preferred Term

Analysis Set: Evaluable	PRU 2 mg (N = 278)
Safety Outcome	n (%)
Total no. subjects with adverse events	97 (34.9)
Nervous system disorders	51 (18.3)
Headache	33 (11.9)
Dizziness	22 (7.9)
Gastrointestinal disorders	45 (16.2)
Diarrhoea	14 (5.0)
Nausea	14 (5.0)
Abdominal pain upper	8 (2.9)
Abdominal distension	7 (2.5)
Abdominal pain	6 (2.2)
Cardiac disorders	11 (4.0)
Palpitations	6 (2.2)

Note: Percentages calculated with the number of subjects in PRU group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AEs are coded using MedDRA version 19.1.

Severe TEAEs were reported in 7 subjects and the most frequently reported severe events were similar as the most frequently reported events (headache, dizziness). The investigators considered most of the severe TEAEs as related to study drug.

No death was reported in the study. One serious TEAE was reported in this study. One subject who had ongoing medical history of extrasystoles at study entry, experienced a treatment emergent serious AE (ventricular extrasystoles). No action was taken with the study drug and investigator considered the event as not related to the study drug. The outcome was reported as 'resolving/recovering' at the time of data-lock date.

Eleven subjects experienced treatment emergent cardiac disorders. The most frequently reported cardiac disorder was palpitation (6 subjects), followed by ventricular extrasystoles (2 subjects). Arrhythmia, extrasystoles, and tachycardia was reported in 1 subject each. One event of ventricular extrasystoles was considered serious by the investigator. The outcome of all events, except the SAE of ventricular extrasystoles, was reported as 'resolved' at the time of data-lock date.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): In this open-label, single arm study which enrolled Chinese female subjects using PEG or lactulose for their CC condition without getting adequate relief, a statistically significant number of subjects responded to prucalopride 2-mg treatment (defined as increase in at least 1 SCBM/week compared to baseline) over the 12-week Treatment Phase (primary efficacy endpoint). The percentage of responders was 74.1%, which was 39.1% higher than the predefined expected response rate of 35%. More than half of the subjects (55.4%) reported ≥3 normal SCBMs/week during the Treatment Phase. Once daily administration of prucalopride 2-mg showed a rapid onset of action and the significant treatment effects were maintained throughout the 12-week Treatment Phase. The therapeutic benefit of prucalopride 2-mg was also demonstrated by the reduced rescue laxative/enema use, improvement in consistency of BMs, improved constipation-related bowel symptoms and quality of life in this study. Overall, the safety profile was consistent with the known profile for prucalopride, with no new or unexpected safety signals.

Collectively, these data demonstrated a favorable benefit-risk profile of prucalopride for the treatment of Chinese female subjects with CC who had failed to respond to laxative treatment.

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