SYNOPSIS

Name of Sponsor/Company	Xian Janssen Pharmaceutical Ltd.
Name of Investigational Product	JNJ-17296812-AAA (Domperidone)

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Prepared by: Janssen Research & Development

Protocol No.: R033812DYP4002

Title of Study: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Prospective Pilot Study to Preliminarily Evaluate the Efficacy of Domperidone in Adult Chinese Subjects with Functional Dyspepsia

NCT No.: NCT03617016 (pre-registered)

Clinical Registry No.: CR108512

Coordinating Investigator(s): Xiucai Fang, MD - Peking Union Medical College Hospital, PPD China

Study Center(s): 5 sites in China

Publication (Reference): None

Study Period: 27 Aug 2018 (Date first subject signed informed consent) to 31 Jul 2020 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 4

Objectives: The primary objective was to explore the efficacy of domperidone with the primary endpoint as the response rate based on overall treatment effect (OTE) on Day 14 in treatment of FD in Chinese patients and identify sub-populations (subtype of the disease) who were sensitive to domperidone treatment. Secondary objectives were to explore the effect in each individual symptom of FD and the change of FD-related quality of life (QoL) with domperidone treatment. The secondary endpoints of this study included response rate based on OTE on Day 7, percentage of subjects with each average symptom score decreased at least 2 points compared to baseline, weekly change in frequency of each FD symptom from baseline and QoL evaluation using the Nepean Dyspepsia Index (NDI).

Methodology: This was a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group, prospective pilot study conducted in China that preliminarily evaluated the efficacy of domperidone in adult Chinese subjects with FD. Subjects aged 18 to 60 years who had FD according to Rome IV diagnostic criteria that met all of the inclusion criteria and none of the exclusion criteria were randomly assigned in a 1:1 ratio to the domperidone or placebo treatment group.

After signing informed consent form (ICF), subjects entered a 7-day screening period, symptom evaluation data collected during this period were used as baseline value. In the following double-blind treatment period, domperidone 10 mg tablets or matching placebo tablets were administered orally 3 times daily before meals for 14 days. Subjects were asked to return to the study site on Day 15 for end-of-study assessments. The duration of each subject's participation was approximately 3 weeks.

Subjects were followed for efficacy and safety as per the Time and Events Table in the protocol. The efficacy evaluations included the OTE, symptoms evaluation scale, and the NDI-QoL. Safety evaluations

included the monitoring of AEs, vital sign measurements, physical examinations, clinical laboratory tests, and 12-lead electrocardiograms (ECGs).

Number of Subjects (planned and analyzed):

In total, there were 160 subjects randomly assigned to treatment (80 subjects to the domperidone treatment group and 80 subjects to the placebo treatment group). All 160 subjects were in modified intent-to-treat (mITT) analysis set and safety population set. There were 148 subjects including 73 subjects in domperidone group and 75 subjects in placebo group for per-protocol analysis set.

Diagnosis and Main Criteria for Inclusion: The subject population consisted of Chinese adult subjects aged 18 to 60 years who met the diagnostic criteria for FD (postprandial distress syndrome [PDS] and/or epigastric pain syndrome [EPS]) according to Rome IV diagnostic criteria for functional gastrointestinal disorders; had a upper endoscopy performed within 3 months before or during the screening period that showed no evidence of structural disease that was likely to explain the dyspepsia symptoms.

Test Product, Dose and Mode of Administration, Batch No.: Domperidone 10 mg tablets were supplied by the sponsor. Subjects were instructed to take one tablet orally 3 times daily 15-30 minutes before meals. Each dose was taken 4-6 hours apart and swallowed in its entirety without dissolving it in water. The batch number was 18031985.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matched placebo tablets were supplied by the sponsor. One tablet was taken orally 3 times daily 15-30 minutes before meals. Each dose was taken 4-6 hours apart and swallowed in its entirety without dissolving it in water. The batch number was 18031784.

Duration of Treatment: After randomization, subjects were treated for 14 days with domperidone or placebo with last visit on Day 15.

Criteria for Evaluation: The efficacy evaluations included OTE, symptoms evaluation scale, and the NDI-QoL.

On Days 7 and 14, subjects were asked to complete the OTE assessment. Subjects with “extremely improved” or “improved” were considered as responders. Response rate of OTE was defined as the percentage (%) of responder in subjects.

During Screening and Treatment phase, subjects were asked to rate the severity of each FD symptoms daily. For each FD symptom, the percentage of subjects with average symptom score (average of Day 1 through Day 7 as the 1st treatment week and Day 8 through Day 14 as the 2nd treatment week) decreased at least 2 points compared to baseline (including subjects with average symptom score of 2 at baseline and average score of 1 during the 1st treatment week and the 2nd treatment week) was calculated. The weekly frequency of symptoms with at least 5 points on severity was also calculated based on the symptom severity data weekly. Changes of frequency with specific symptoms were summarized.

The NDI questionnaire was used on Days -1 and 15 to assess the effects of treatment on disease-specific QoL. Data of OTE assessment, symptoms evaluation data were collected using electronic diaries. NDI-QoL data were collected using paper questionnaire.

Safety Evaluation: Any clinically relevant changes occurring during the study was recorded on the Adverse Event section of the case report form. Any clinically significant abnormalities persisting at the end of the study/early withdrawal was followed by the investigator until resolution or until a clinically stable endpoint was reached.

The evaluations of safety and tolerability study included adverse event (AE) monitoring, clinical laboratory tests, ECG, vital signs, and physical examinations according to the time points specified.

Statistical Methods: This was a pilot study and enrolled 160 subjects. The sample size was not based on statistical calculation.

Primary efficacy analyses were performed on the modified intent-to-treat (mITT) population. The primary endpoint was defined as the response rate of OTE evaluated on Day 14. The response rate was summarized using the number of observations and percentages by treatment group. Relative risk (RR) was provided using Cochran-Mental-Haenszel (CMH) method stratified by FD types. Analysis of the primary endpoint was also performed based on the PP population for sensitivity analysis.

The response rate on the OTE on Day 7 was summarized using the number of observations and percentages by treatment group as appropriate. The percentage of subjects with average symptom score (average of Day 1 through Day 7 as the 1st treatment week and Day 8 through Day 14 as the 2nd treatment week) decreased at least 2 points compared to baseline (including subjects with average symptom score of 2 at baseline and average score of 1 during the 1st treatment week and the 2nd treatment week) was summarized using the number of observations and percentages by treatment group as appropriate. The symptom frequency assessment was summarized using the number of observations, mean, standard deviation (SD), median, and range by treatment group as appropriate.

The change from baseline of the NDI-QoL was summarized using the number of observations, mean, SD, median, and range by treatment group as appropriate.

The safety analyses included all subjects who signed informed consent, randomized, and received at least 1 dose of the study drug. All reported adverse events were summarized. The impact on ECG was assessed using descriptive statistics and frequency tables. Descriptive statistics of vital signs and changes from baseline were summarized at each scheduled time point. Results of the physical examination were listed.

RESULTS:

STUDY POPULATION:

Of the 211 subjects screened for the study, 160 subjects were enrolled in 1:1 randomization to receive 10 mg study drug domperidone three times daily or matching placebo. One subject in domperidone group and two subjects in placebo group discontinued study agent, one subject in domperidone group and three subjects in placebo group terminated study participation prematurely. No patients were unblinded during the study, all patients randomized received treatment.

The demographic characteristics were comparable across treatment groups. The study population consisted of Chinese patients. The median age was 30.5 years (range 19 to 56 years) in domperidone group and 29.0 years (range 20 to 59 years) in placebo group. There were 49 (61.3%) subjects in domperidone group and 51 (63.8%) subjects in placebo group who were female.

By FD subtypes, 41 (51.3%) subjects in domperidone group were PDS, 6 (7.5%) were EPS and 33 (41.3%) were overlapping PDS and EPS, while in placebo group subjects with PDS, EPS and with overlapping PDS and EPS subtypes were 41 (51.3%), 5 (6.3%) and 34 (42.5%) respectively.

In placebo group, 9 (11.3%) subjects were co-treated with concomitant medication, while in domperidone group 3 (3.8%) subjects were.

In domperidone group, 9 (11.3%) subjects were reported with major protocol deviations: 2 (2.5%) entered but did not fulfill inclusion criteria, 2 (2.5%) received a disallowed concomitant treatment, no subjects received wrong treatment or incorrect dose nor developed withdrawal criteria but not withdrawn, 5 (6.3%) subjects had other reasons in domperidone group. In placebo group, 7 (8.8%) subjects were reported with 9 major protocol deviations: 2 (2.5%) entered but did not fulfill inclusion criteria, 1 (1.3%) received a disallowed concomitant treatment, 2 (2.5%) received wrong treatment or incorrect dose, 1 (1.3%) developed withdrawal situation but not withdrawn, 3 (3.8%) other reasons. Two subjects in placebo group were

reported with two categories of major protocol deviations, including one subject with receiving a disallowed concomitant treatment and receiving wrong treatment or incorrect dose, another subject with developing withdrawal situation but not withdrawn and other reason.

All subjects received the study drug with the overall treatment compliance > 95%. The median of the total duration of exposure in domperidone group was 14.0 days (range 13 to 15 days), while 14.0 days (range 7 to 15 days) in placebo group. The number of doses taken in each study treatment group was similar.

EFFICACY RESULTS:

R033812DYP4002 was a pilot study with primary objective to explore the efficacy of domperidone in treatment of FD in Chinese patients and identify sub-populations (subtype of the disease) who respond to domperidone treatment.

- Overall, a numerical improvement in **OTE response rate** on Day 14 in Chinese FD subjects as 60.7% versus 46.0% with RR of 1.318 (95% confidence interval [CI]: 0.972, 1.787) in domperidone group compared to placebo group in modified intent-to-treat set (mITT) analysis set. And the OTE response rate on Day 14 was 61.6% versus 45.3% with RR of 1.361 (95% CI: 1.001, 1.850) in domperidone group compared to placebo group in PP analysis set.
- By **FD subtype**, domperidone was also observed with a numerical improvement of OTE response rate on Day 14 compared to placebo in subtype of PDS as 60.3% versus 54.9% with RR of 1.098 (95% CI: 0.750, 1.607), in subtype of EPS as 64.3% versus 46.2% with RR of 1.412 (95% CI: 0.416, 4.793) and in overlapping PDS and EPS as 60.6% versus 35.2% with RR of 1.722 (95%CI: 0.995, 2.980). Results of EPS should be interpreted with caution due to a small number of subjects (less than 6 subjects) in each group.
- Domperidone showed no significant difference of OTE on Day 7 as 32.0% versus 35.9% in domperidone group and placebo group, with the RR of 0.891 (95% CI: 0.574, 1.383).
- During the **1st treatment week** (Day 1 through Day 7), domperidone was observed with more numerical decreases in Global Symptom Scale (GOS) severity (decreasing at least 2 points compared to baseline) compared to placebo in FD symptoms as epigastric pain, epigastric bloating and nausea, and on decreasing GOS frequency (frequency change with at least 5 points from baseline) in FD symptoms as postprandial fullness, early satiation, epigastric burning, epigastric bloating, nausea and vomiting. During the **2nd treatment week** (Day 8 through Day 14), domperidone was observed with more numerical decreases in GOS severity compared to placebo in postprandial fullness, early satiation, belching, epigastric bloating, nausea and vomiting, and in GOS frequency in postprandial fullness, epigastric pain, epigastric burning, belching, nausea and vomiting.
- Subjects in domperidone group showed more numerical decreases in NDI-QoL in total score and each sub-scale at the end of trial (EOT) compared to placebo group. The mean (SD) changes of NDI-QoL from baseline to EOT were -0.1695 (0.15508) versus -0.1279 (0.12059) for domperidone versus placebo in total score, -0.1638 (0.17624) versus -0.1255 (0.12930) in interference, -0.1892 (0.15909) versus -0.1341 (0.13527) in knowledge/control, -0.1876 (0.19100) versus -0.1463 (0.16021) in eat/drink, and -0.1375 (0.22290) versus -0.1058 (0.18251) in sleep disturbance sub-scale.
- An exploratory analysis was performed on subjects with three subgroups by baseline GOS categories ("≤3", ">3 and ≤5", and ">5 and ≤7").
  - Among subjects with average baseline scores **≤3**, domperidone was observed with more numerical decreases in GOS severity compared to placebo in FD symptoms as epigastric burning and belching during **the 1st treatment week**, and in epigastric burning, belching, epigastric bloating, nausea and vomiting during **the 2nd treatment week**.
  - Among subjects with average baseline scores "**>3 and ≤5**", domperidone was observed with more numerical decreases in GOS severity compared to placebo in FD symptoms as epigastric pain,

belching, epigastric bloating and nausea during **the 1st treatment week**, and in postprandial fullness, early satiation, belching, epigastric bloating and nausea during **the 2nd treatment week**.

- Results for nausea and vomiting in subjects with average baseline scores ">3 and ≤5" should be interpretated with caution due to a small number of subjects (n≤15 in placebo or domperidone group). No conclusion was derived for subjects with baseline GOS >5 and ≤7 due to a small number of subjects.

- An exploratory analysis was applied by including subjects who "slightly improved" into definition of response and excluding subjects who "improved" from definition of response. Per definition of response rate as extremely improved and as combination of extremely improved, improved and slightly improved, OTE response rate was 24.6% versus 18.5% with RR of 1.317 (95% CI: 0.712, 2.434) and 91.7% versus 85.2% with RR of 1.075 (95% CI: 0.957, 1.207) respectively.
- Four post-hoc analyses were performed using mITT analysis set on subjects with moderate to severe FD symptoms defined as symptom scores at least once with severity score **≥5 or ≥4** at baseline.
  - Among subjects with symptom scores **at least once severity score ≥5** at baseline, domperidone was observed with more numerical decreases in GOS severity compared to placebo in FD symptoms as epigastric pain, belching, epigastric bloating and vomiting and in GOS frequency in postprandial fullness, early satiation, epigastric burning, belching, epigastric bloating, nausea, and vomiting during **the 1st treatment week**, and in GOS severity in postprandial fullness, early satiation, epigastric pain, belching, epigastric bloating, nausea and vomiting and in GOS frequency in postprandial fullness, early satiation, epigastric burning, belching, nausea and vomiting during **the 2nd treatment week**.
  - Among subjects with symptom scores at least once severity score **≥4** at baseline, domperidone was observed with more numerical decreases in GOS severity compared to placebo in FD symptoms as epigastric pain, belching, epigastric bloating and nausea and in GOS frequency in postprandial fullness, early satiation, epigastric burning, belching, epigastric bloating, nausea, and vomiting during **the 1st treatment week**, and in GOS severity in postprandial fullness, early satiation, epigastric pain, belching, epigastric bloating and nausea, and on decreasing GOS frequency in postprandial fullness, epigastric pain, epigastric burning, belching, epigastric bloating, nausea and vomiting during **the 2nd treatment week**.
- A post-hoc analysis was also performed on NDI-QoL with subjects divided into two subgroups for each NDI-QoL sub-scale with the cutoff value of median baseline index. For subjects with baseline NDI-QoL score above or equal to cutoff value as subgroup with lower life quality, treatment with domperidone was observed with more numerical decreases in NDI-QoL compared to placebo group in total score (-0.2500 versus -0.1948) as mean EOT change from baseline for domperidone and placebo group, and each sub-scale including eat/drink (-0.2701 versus -0.1993) as mean EOT change from baseline ; for subjects with lower baseline NDI-QoL score as subgroup with higher life quality, treatment with domperidone was observed with a more numerical decrease in NDI-QoL total score only (-0.0759 versus -0.0705) compared to placebo.
- Two post-hoc analyses were performed using mITT analysis set on subjects by FD subtypes on each FD symptom.
  - Among subjects **by PDS** as FD subtype, domperidone was observed with more numerical decreases in GOS frequency compared to placebo in postprandial fullness, early satiation, belching, epigastric bloating, nausea and vomiting during **the 1st treatment week**, and in GOS severity compared to placebo in epigastric bloating and nausea, and in GOS frequency in postprandial fullness, early satiation, belching, epigastric bloating, nausea and vomiting during **the 2nd treatment week**.

  - Among subjects **by overlapping PDS and EPS** as FD subtype, domperidone was observed with numerical more decreases in GOS severity compared to placebo in FD symptoms as in early satiation, epigastric pain, epigastric bloating, nausea and vomiting, and in GOS frequency in postprandial fullness, early satiation, epigastric burning and nausea during **the 1st treatment week**, and in GOS severity in postprandial fullness, early satiation, belching, nausea and vomiting, and in GOS frequency in postprandial fullness, epigastric pain, epigastric burning, belching and nausea during **the 2nd treatment week**.
  - GOS severity and frequency of **EPS** as FD subtype were not explored due to a limited sample size (n=6 in domperidone group and n=5 in placebo group respectively).

- In post-hoc analysis performed in subjects **by FD subtype defined by baseline (Day -7 through Day -1) GOS scores**, domperidone was observed with a numerically higher OTE response rate on Day 14 compared to placebo in PDS subjects as 65.0% versus 43.7% with RR of 1.486 (95% CI: 0.835, 2.644), in overlapping PDS and EPS as 57.1% versus 50.7% with RR of 1.126 (95% CI: 0.776; 1.632), and not applicable for EPS with limited sample size (less than 5 in each group).
- Two post-hoc analyses were performed using mITT analysis set on subjects by FD subtype defined by baseline (Day -7 through Day -1) GOS scores.
  - Among subjects of **PDS subtype defined by baseline (Day -7 through Day -1) GOS scores**, domperidone was observed with more numerical decreases in GOS severity compared to placebo in epigastric bloating and in GOS frequency in postprandial fullness and nausea during **the 1st treatment week**, and in GOS severity in epigastric bloating and nausea and in GOS frequency in postprandial fullness and nausea during **the 2nd treatment week**.
  - Among subjects of **overlapping PDS and EPS subtype defined by baseline (Day -7 through Day -1) GOS scores**, domperidone was observed with more numerical decreases in GOS severity compared to placebo in early satiation, epigastric pain, nausea and vomiting, and in GOS frequency in postprandial fullness, early satiation, epigastric bloating, nausea and vomiting during **the 1st treatment week**, and in GOS severity in postprandial fullness, early satiation, epigastric pain, belching, epigastric bloating, nausea and vomiting, and in GOS frequency in postprandial fullness, early satiation, epigastric pain, epigastric burning, epigastric bloating, nausea and vomiting during **the 2nd treatment week**.
  - GOS severity and frequency of **EPS subtype defined by baseline (Day -7 through Day -1) GOS scores** were not explored with a limited sample size (less than 5 in each group).

SAFETY RESULTS:

- A total of 7 subjects (8.8%) in the domperidone group and 12 subjects (15.0%) in placebo group were reported with 1 or more treatment-emergent adverse events (TEAEs). Gastrointestinal disorders (4 [5.0%] in domperidone group and 3 [3.8%] in placebo group), infections and infestations (1 [1.3%] in domperidone group and 2 [2.5%] in placebo group) were the most frequently reported system organ classes (SOCs).
- Only one serious TEAE was reported which was in placebo group and was considered not related to study agent.
- A total of 4 (5.0%) TEAEs were reported as related to domperidone by the investigator, including one subject experienced cardiovascular AE in severity of mild, and no new safety signals were identified in the study.
- No deaths, no AEs leading to discontinuation of study agent, no AEs leading to termination of study participation, no AEs leading to dose interruption or dose modification occurred during the study.

- No additional safety signals were identified from vital signs or physical findings.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

- Domperidone showed a positive trend in FD treatment as a numerical higher OTE response rate on Day 14 compared to placebo, but no observable trend in OTE response rate on Day 7.
- Domperidone also showed a positive trend in FD subjects with subtype of PDS, EPS and overlapping PDS and EPS on Day 14.
- Domperidone was observed with more numerical decreases in severity level and frequency of most FD symptoms during Day 8 through Day 14 compared to placebo, from which the PRO evaluated by GOS score showed consistent with OTE evaluation from investigator's side and showed numerical more decreases in NDI-QoL in total score and each sub-scale at the EOT compared to placebo group.
- There were no deaths, no AEs leading to discontinuation of study agent, no AEs leading to termination of study participation, no AEs leading to dose interruption or dose modification. Domperidone 10 mg tablets administered 3 times was well tolerated in subjects with FD in 2 weeks. The safety profile of the study was consistent with established safety profile of domperidone, and no new safety signals were identified in this study.

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