SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	Resolor™
Name of Active Ingredient(s)	Prucalopride Succinate

Protocol No.: PRUCRC3001

Title of Study: A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor®) Tablets in Subjects with Chronic Constipation

NCT No.: Not applicable.

Clinical Registry No.: Not applicable.

Coordinating Investigators: Meiyun Ke, MD - Peking Union Medical College Hospital, Beijing, China

Study Center(s): Forty-six centers in 5 countries/regions, including Australia (8 centers); China (19 centers); South Korea (12 centers); Taiwan (3 centers); and Thailand (4 centers).

Publication (Reference): None.

Study Period: 02 April 2010 to 09 March 2011.

Phase of Development: 3.

Key Objectives: The primary objective of this study was to demonstrate that prucalopride 2 mg (succinate salt R108512), given orally once daily for 12 weeks, is more effective than placebo in treatment of chronic constipation in subjects as measured by the percentage of subjects with a weekly average of 3 or more spontaneous complete bowel movements (SCBMs) (responders) during the 12-week double-blind treatment phase. The key secondary objective was to demonstrate that treatment with prucalopride 2-mg given orally once daily for 4 weeks is more effective than placebo as measured by the percentage of subjects with a weekly average of 3 or more SCBMs (responders) during the first 4 weeks of the double-blind treatment phase.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study with a parallel-group design, consisting of 3 phases: a 2-week drug-free screening/run-in phase, a 12-week, double-blind, placebo-controlled treatment phase, and a posttreatment follow-up contact performed 7 days following the last dose of study drug. During the run-in phase, the subject's bowel habit was documented and the existence of chronic constipation confirmed. At the start of this phase, all existing laxative medication was withdrawn and subjects were instructed not to change their diet or lifestyle during the study. Subjects were allowed to take a laxative (bisacodyl) as a rescue medication throughout the study, but only if they have not had a bowel movement (BM) for 3 or more consecutive days. If subject was unable to tolerate bisacodyl, an enema may have been used in place of the bisacodyl. No bisacodyl was taken or enemas used within 48 hours before or after the first dose of study drug in the double-blind treatment phase (ie, 1 day before Visit 2 to 3 days after Visit 2). Subjects entered the double-blind treatment phase if constipation was shown to be present during the run-in phase. During the double-blind treatment phase, subjects were treated for 12 weeks with prucalopride 2 mg or matching placebo, given orally once daily before breakfast. Subjects recorded study drug and rescue medication dosing

information and information related to BMs in a daily diary throughout the study. Subjects were required to complete global assessments (ie, consistency of stool by Bristol Stool Scale; global evaluation of severity of constipation; global evaluation of efficacy of treatment) and the PAC-SYM, PAC-QOL, and SF-36 (Acute) questionnaires at specified visits. The investigator provided a global assessment of efficacy of treatment. Subject safety was monitored throughout the study.

Number of Subjects (planned and analyzed): The planned sample size in this study was 500 subjects; 774 subjects were screened in the study and 507 subjects (253 prucalopride and 254 placebo) were randomized into the two treatment groups in the study. The intent-to-treat (ITT) analysis set included the 501 randomized subjects (249 prucalopride, 252 placebo) who received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion: Men and women from the Asia-Pacific region with chronic constipation, aged 18 to 65 years, inclusive were to be included in this study. A history of chronic constipation, defined as ON AVERAGE, 2 OR FEWER SPONTANEOUS BOWEL MOVEMENTS (SBMs) PER WEEK AND 1 OR MORE of the following for at least a quarter of the time for the last 3 months was required: very hard and/or hard stools, sensation of incomplete evacuation, stratining at defecation, sensation of ano-rectal obstruction or blockade, and/or need for digital manipulation to facilitate evacuation, with no SBMs during the run-in phase (subject was then considered to be constipated and eligible to participate). Constipation was to be functional and not drug-induced, with no secondary causes of chronic constipation eg, endocrine, metabolic, or neurological disorders, surgical obstruction, megacolon/megarectum, diagnosis of pseudo-obstruction. Subjects were to have no known or suspected organic disorders of the large bowel, ie, obstruction, carcinoma, or inflammatory bowel disease. Results of a barium enema or of a colonoscopic examination performed within the past 1 year were required to rule out organic disorders. Acolonoscopic examination performed within the last 3 years was acceptable if the examination was performed for evaluation of constipation and there was no history or evidence of weight loss, anemia, or rectal bleeding. Subjects who had polyps discovered on the colonoscopy that were untreated (ie, by polypectomy) were to be excluded from the study. Subjects were to have no severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or acquired immune deficiency syndrome, or other gastrointestinal or endocrine disorders.

Test Product, Dose and Mode of Administration, Batch No.: Prucalopride 2-mg tablet batch numbers were B119848 and B124992 of Lot Number 9KL1R.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo batch numbers were B119848 and B124992 of Lot Number 9KL1W.

Duration of Treatment: The study consisted of 3 phases: a 2-week drug-free screening/run-in phase, a 12-week, double-blind, placebo-controlled treatment phase, and a posttreatment follow-up contact performed 7 days following the last dose of study drug. The total duration of the subject's participation in the study was approximately 15 to 20 weeks, including the run-in and posttreatment phases.

Criteria for Evaluation: Efficacy evaluations included information on BMs and use of bisacodyl/enema recorded on the subject's diary. Additional efficacy evaluations included subject's global assessments (ie, consistency of stool by Bristol Stool Scale, severity of constipation, and efficacy of treatment), the investigator's global assessment on efficacy of treatment, and the PAC-SYM, PAC-QOL, and SF-36 (Acute) questionnaires. The primary efficacy endpoint was the percentage of subjects with an average of 3 or more SCBMs per week (responders) during the entire 12-week double-blind treatment phase. The key secondary endpoint was the percentage of subjects with an average of 3 or more SCBMs per week (responders) during the first 4 weeks of the double-blind treatment phase.

Other secondary efficacy endpoints, based on data collected on diaries and questionnaires, included the percentage of subjects with an average increase of 1 or more SCBMs per week; average number of SCBMs, SBMs, and all BMs per week; time-to-first SCBM/SBM and time-to-first week with 3 or more SCBMs after the first dose of the study drug; average number of bisacodyl tablets taken and its reduction per week; percentage of BMs per week with normal consistency (Types 3-4 based on Bristol Stool Scale), with less straining, and with a sense of complete evacuation; changes from baseline in subject's global assessments and PAC-SYM scores; and the investigator's global assessment on efficacy of treatment. Exploratory efficacy endpoints included changes from baseline in the PAC-QOL and SF-36 (Acute) scores. Safety was evaluated by the monitoring of the frequency, severity, and timing of adverse events, clinical laboratory test results, 12-lead ECG recordings, vital signs measurements, and physical examinations.

Statistical Methods: Sample size estimation for this study was based on the assumption that the between treatment difference in the primary endpoint is 12.3% (with 15% responders from the placebo group and 27.3% from the 2-mg group in the Asian population). The study needed a sample size of 237 subjects per group to detect this difference with approximately 90% power (for a 2-sided test at 5% significance level). It was assumed that approximately 5% of the subjects would have insufficient diary data to be evaluated as a responder in the ITT analysis set for the 12-week double-blind treatment phase, 500 subjects were needed to be randomized to the 2 treatment groups (with 250 in each group) to adjust for this dropout rate. The actual number of randomized subjects was 507 (254 placebo, 253 prucalopride 2 mg), of whom 501 received study drug and were included in the ITT analysis set (252 placebo, 249 prucalopride 2 mg).

The primary endpoint was the percentage of subjects with an average of 3 or more SCBMs per week (responders) during the entire 12-week double-blind treatment phase. A Cochran-Mantel-Haenszel chi-square test for general association between the treatment and response during the 12-week double-blind treatment phase was performed, controlling for the effects of country/region and the baseline severity of constipation. The between treatment group difference in percentage of responders and the 95% confidence interval (CI) for the difference was estimated based on the normal approximation to the difference of 2 binomial proportions without continuity correction. Similar statistical methods were used for the key secondary endpoint (response in the first 4 weeks of the study).

Safety was evaluated by examining the incidence and types of adverse events, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital sign measurements from the screening phase through study completion. Descriptive statistics of corrected QT (QTc) intervals and changes from baseline were summarized at each scheduled time point to detect individual QTc changes.

The ITT analysis set was the primary analysis set for all demographic, efficacy, and safety data analyses. A total of 55 subjects in the ITT analysis set were excluded from the per-protocol analysis set due to major protocol violations and missing data based on definitions specified in the Statistical Analysis Plan prior to database unblinding. An analysis of the primary and key secondary efficacy endpoints were performed based on the per-protocol analysis set to corroborate the results for the ITT analysis set.

RESULTS:

STUDY POPULATION:

Of the 501 randomized subjects who took at least 1 dose of study drug, 462 (92.2%) completed the 12-week double-blind treatment phase, including 231 (91.7%) in the placebo group and 231 (92.8%) in the prucalopride 2-mg group. The 501 randomized and treated subjects were distributed across the following 5 countries/regions: China-Chinese (n=313, 62.5%), South Korea (n=93, 18.6%), Australia (n=39, 7.8%), Thailand (n=31, 6.2%), and Taiwan-Chinese (n=25, 5.0%). A higher percentage of subjects

in the prucalopride 2-mg group (3.2%) withdrew due to adverse events compared with the placebo group (1.2%), while more subjects in the placebo group were discontinued for lack of efficacy (2.4% vs 0% in prucalopride group) or withdrawal of consent (3.2% vs 1.2% in prucalopride group).

In general, the demographic and baseline characteristics of subjects in the placebo and prucalopride 2-mg groups appeared similar. The 501 subjects comprising the ITT analysis set were predominately female (89.8%) and Asian (92.4%), and had a mean age of 41.6 years. At screening, subjects reported an average of 1.1 SBM/week (44.3% reported <1 SBM/week), and using bisacodyl or an enema an average of 1.0 days/week. Most subjects reported prior laxative/enema use (n=360, 71.9%); use of these treatments was reported as inadequate for 277/360 (76.9%) subjects.

Exposure to study drug appeared similar for the 2 treatment groups. The average number of days of dosing was 79.47 days in the placebo group and 79.63 days in the prucalopride 2-mg group. Approximately 92% of subjects in each treatment group were at least 75% treatment compliant (ie, received ≥ 63 days of study drug treatment).

EFFICACY RESULTS: The percentage of subjects in the ITT analysis set with an average of ≥3 SCBMs per week during the entire 12-week double-blind phase (responders) was significantly ($p<0.001$) higher for the prucalopride 2-mg group (n=83, 33.3%) compared with the placebo group (n=26, 10.3%) (between-group difference of 23%). Thus, the primary study objective was achieved. Results of analyses of the key and other secondary endpoints were consistent with those of the primary endpoint in showing that the clinical improvement in the prucalopride 2-mg group was larger, and generally statistically significantly superior, to that seen in the placebo group. Results from the per-protocol analysis were consistent with those based on the ITT analysis set for the primary and key secondary efficacy endpoints. The median time to the first SCBM or first SBM after the first dose of study medication was significantly shorter in the prucalopride 2-mg group (1.56 and 0.10 days, respectively) compared with the placebo group (12.58 and 1.60 days) ($p<0.001$ for both).

Results of Selected Efficacy Endpoints (Intent-to-Treat Analysis Set)

Endpoint	Placebo (N=252)		PRU 2 mg (N=249)		Overall P-value	PRU 2 mg Minus Placebo
	N	n (%)	N	n (%)		Diff (%) (95% CI)
Primary Endpoint						
≥ 3 SCBMs/wk, Wks 1-12	252	26 (10.3)	249	83 (33.3)	<0.001[a]	23.0 (16.1;30.0)
Other Endpoints						
≥ 3 SCBMs/wk, Wks 1-4	252	28 (11.1)	249	86 (34.5)	<0.001[a]	23.4 (16.4;30.5)
INC ≥ 1 SCBMs/wk, Wks 1-12	248	68 (27.4)	243	139 (57.2)	<0.001[a]	29.8 (21.4; 38.1)
Impr ≥ 1 PAC-SYM overall score, Wk 12 (LOCF)	249	42 (16.9)	249	86 (34.5)	<0.001[a]	17.7 (10.2;25.2)
Impr ≥ 1 PAC-QOL, Wk 12 (LOCF)						
Overall score	247	41 (16.6)	248	92 (37.1)	<0.001	20.5 (12.9; 28.1)
Dissatisfaction score	247	55 (22.3)	248	117 (47.2)	<0.001	24.9 (16.8; 33.0)
Subject ratings at Wk 12 (LOCF)						
Efficacy of treatment (quite a bit/extremely effective)	249	22 (8.8)	249	82 (32.9)	<0.001[a]	24.1 (17.3, 30.9)
Severity of constipation (absent/mild)	249	68 (27.3)	249	133 (53.4)	<0.001[a]	26.1 (17.8, 34.4)
Inv. ratings at Wk 12: (LOCF) Efficacy (quite at bit/extremely effective)	247	34 (13.7)	247	101 (40.8)	<0.001[b]	N/A
Change from baseline, Wks 1-12	N	Mean (SD)	N	Mean (SD)	P-value	LS Mean Diff (95% CI)
AVG bisacodyl/wk:	236	-0.3 (1.54)	233	-1.0 (1.50)	<0.001[c]	-0.7 (-0.94; -0.45)
AVG enema/wk	236	0.0 (0.25)	233	-0.0 (0.26)	<0.001[c]	-0.1 (-0.11; -0.33)
AVG days with bisacodyl/wk	236	-0.2 (0.82)	233	-0.6 (0.75)	<0.001[c]	-0.3 (-0.44, -0.21)
AVG days with bisacodyl or enema/wk	236	-0.2 (0.82)	233	-0.6 (0.78)	<0.001[c]	-0.4 (-0.47, -0.24)

AVG = average; CI = confidence interval; Diff = difference; Impr = improvement; INC = increase; Inv = investigator; LOCF = last observation carried forward; LS = least squares; SCBM = spontaneous complete bowel movement; SD = standard deviation; Wk = week

[a] Generalized Cochran-Mantel Haenszel test for general association controlling for country/region, baseline severity.

[b] Van Elteren test controlling for country/region and baseline severity.

[c] Test for no difference between treatments from ANCOVA model with factors for treatment, baseline, country/region, baseline severity (type III SAS).

SAFETY RESULTS:

The percentages of subjects with treatment-emergent adverse events (TEAE) and adverse events assessed by the investigator as study drug-related were higher for the prucalopride 2-mg group than for the placebo group.

Subjects With Treatment-Emergent Adverse Events (Intent-to-Treat Analysis Set)

	Placebo (N=252) n	(%)	PRU 2 mg (N=249) n	(%)
One or more adverse events	92	(36.5)	142	(57.0)
One or more serious adverse events	5	(2.0)	3	(1.2)
Deaths	0		0	
Discontinuation due to adverse events	3	(1.2)	8	(3.2)
Adverse events of interest	4	(1.6)	5	(2.0)

In the prucalopride 2-mg group, the most frequently reported TEAEs, and study drug-related TEAEs, were diarrhea, headache, nausea, and abdominal pain. Most TEAEs were mild or moderate in intensity; diarrhea and headache were the only adverse events assessed as severe in >1% of subjects in the prucalopride 2-mg group (4.8% and 2.0%, respectively). Adverse events of interest (palpitations, cardiovascular ischemic events) occurred at a similar, low rate in the prucalopride 2-mg and placebo groups.

There were no deaths in the study. Treatment-emergent serious adverse events (SAEs) occurred in a similar percentage of subjects receiving prucalopride 2 mg or placebo. Two of the 3 SAEs in the prucalopride 2-mg group were assessed as not related to study drug. A small percentage of subjects in the prucalopride 2-mg (3.2%) or placebo group (1.2%) had treatment-emergent adverse events that led to study discontinuation. Diarrhea and nausea were the most common TEAEs leading to discontinuation among subjects treated with prucalopride, and all but one TEAE leading to discontinuation in the prucalopride group resolved (lichen planus in prucalopride 2-mg group ongoing).

Treatment-Emergent Adverse Events That Occurred in at Least 2% of Subjects in Any Treatment Group (Intent-to-Treat Analysis Set)

Body System Preferred Term	Placebo (N=252) n (%)	PRU 2 mg (N=249) n (%)
Gastrointestinal disorders	**50 (19.8)**	**100 (40.2)**
Diarrhoea	20 (7.9)	55 (22.1)
Nausea	8 (3.2)	29 (11.6)
Abdominal pain	6 (2.4)	17 (6.8)
Abdominal distention	6 (2.4)	7 (2.8)
Abdominal pain upper	6 (2.4)	6 (2.4)
Gastrointestinal sounds abnormal	0	5 (2.0)
Nervous system disorder	**13 (5.2)**	**41 (16.5)**
Headache	5 (2.0)	31 (12.4)
Dizziness	4 (1.6)	5 (2.0)
Infections and infestations	**24 (9.5)**	**27 (10.8)**
Nasopharyngitis	11 (4.4)	7 (2.8)
Upper respiratory tract infection	4 (1.6)	6 (2.4)
Urinary tract infection	5 (2.0)	2 (0.8)
Ear and labyrinth disorders	**1 (0.4)**	**7 (2.8)**
Vertigo	0	6 (2.4)

NOTE: Subjects with multiple occurrences of the same adverse event were counted only once for that particular preferred term or body system.

There were no clinically meaningful findings in laboratory, vital signs, or ECG values, based either on observed changes from baseline or the percentage of subjects with values exceeding pre-defined normal limits. The percentage of subjects with a normal baseline and an abnormal post-baseline value was generally similar for the prucalopride 2-mg and placebo groups for all hematology and blood chemistry

analytes, pulse rate, blood pressure, and corrected QT interval and other ECG parameters. No subject in the prucalopride 2-mg group with a normal baseline value had a post-baseline QTcB or QTcF value prolonged to >480 msec, or a change from baseline in the QTcB or QTcF interval of >60 msec.

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

CONCLUSIONS: In this double-blind, randomized, placebo-controlled study in subjects with chronic constipation, a significantly higher percentage of subjects achieved normalization of BMs, defined as an average of ≥3 SCBMs/week over the 12-week treatment period (primary efficacy endpoint) and during the first 4 weeks of treatment (key secondary endpoint) in the prucalopride 2-mg group. 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 period. The therapeutic benefit of prucalopride 2 mg versus placebo was also demonstrated by the reduced rescue laxative/enema use, improved constipation-related bowel symptoms and quality of life in this study. The results of this study showed that prucalopride was safe and well tolerated in subjects in the Asia Pacific region.

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