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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Relistor® / Methylnaltrexone bromide (MOA-728)

PROTOCOL NO.: 3200A3-200-WW (B2541019)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral MOA-728 for the Treatment of Opioid Induced Bowel Dysfunction in Subjects With Chronic Non-Malignant Pain

Study Centers: A total of 70 centers took part in the study and randomized subjects; 54 in the United States, 8 in Canada, 4 in Korea and 1 each in Sweden, Poland, Hungary, and in Australia.

Study Initiation and Final Completion Dates: August 2006 to February 2007
The study was terminated because of lack of efficacy.

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To establish the dose-response relationship of MOA-728 by observing spontaneous bowel movements in a population of subjects with chronic, non-malignant pain who had opioid induced bowel dysfunction (OIBD), and to establish appropriate doses for confirmatory phase 3 studies;
- To evaluate the safety and tolerability of oral MOA-728 given daily in a population of subjects with chronic, non-malignant pain who have OIBD.

Secondary objectives:

- To evaluate the dose-response relationship of oral MOA-728 on secondary endpoints to support the dose selection for subsequent confirmatory phase 3 studies;
- To evaluate exposure response relationships;
- To explore subject-reported outcomes for perceived benefits of treatment with MOA-728.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized adaptive design study using placebo and 5 active treatment arms (10, 50, 150, 300, 450 mg/day MOA-728) in subjects with chronic non-malignant pain. During the study, a Bayesian algorithm was used to adaptively allocate subjects to the treatment arms based on the observed treatment effect. In addition, 2 interim analyses were performed and the treatment results were examined by a data monitoring committee. The first interim analysis was conditioned on the test article being safe and tolerable based on pre-specified adverse events (AEs), and the second interim analysis was to assess efficacy as well as safety and tolerability. The study team was blinded to the results of the interim analyses. The duration of the study was planned to be approximately 9 months.

Eligible subjects entered a 14-day single-blind, placebo run-in period during which objective evidence of constipation was assessed. Subjects who remained eligible at the Baseline visit were then assigned to either placebo or 1 of 5 active doses for a 28-day, double-blind treatment phase. The 4-week treatment phase was followed by a 14-day post-treatment follow-up period. Thus each subject participated in the study for approximately 8 weeks.

The study flowchart is summarized in Table 1.

Table 1. Study Flowchart

Study Interval	**Placebo Run-In Days –14 to –1**		**Double-Blind Treatment Days 1 to 28**				**Follow-Up**
Study Day	**Day –14[a] (Screening)**	**Day -1**	**Day 1 (Baseline)**	**Day 7[b]**	**Day 14[b]**	**Day 28[b,c]**	**Day 42[b,d]**
Visit ID (for Sponsor use only)	**1**		**2**	**3**	**4**	**5[c]**	**6**
Study Procedures							
Informed consent	X						
Medical history	X						
Pain history	X						
Constipation history	X						
ECOG performance status	X						
Eligibility assessment	X		X				
Randomization			X				
Dispense test article[e]	X		X	X	X		
Placebo run-in test article administration	X----------X						
First dose of double-blind test article			X[f]				
Double-blind test article administration				X----------X			
Completion of dosage record/perform test article accountability			X	X	X	X	
PK blood sample collection			X[g]		X[g,h]	X[g]	
Height	X						
Weight	X		X	X	X	X	X
Physical examination	X					X	X
Vital signs[i]	X		X	X	X	X	X
Laboratory evaluation[j]	X			X	X	X	X
Serum/urine pregnancy test[k]	X		X			X	X
Electrocardiogram[l]	X					X	
Recording of prior/concomitant non-opioid treatments	X		X	X	X	X	X
Recording of opioid treatment	X		X	X	X	X	X
Recording of adverse events[m]	X		X	X	X	X	X
OOWS			X	X	X	X	X
SOWS			X	X	X	X	X
Brief Pain Inventory-Short Form			X		X	X	
Subject diary data[n]							
Bowel movement count[o]	X----------X						
Bristol Stool Form Scale[p]	X----------X						
Straining Scale[p]	X----------X						
Sense of Complete Evacuation[p]	X----------X						
Abdominal Symptoms Scale	X----------X						
Pain Intensity Scale	X----------X						
Appetite Assessment Scale	X----------X						
Rescue laxative/enema use[q]	X----------X						
Opioid use[r]	X----------X						
Health outcomes assessments							

Table 1. Study Flowchart

Study Interval	**Placebo Run-In Days –14 to –1**		**Double-Blind Treatment Days 1 to 28**				**Follow-Up**
Study Day	**Day –14[a] (Screening)**	**Day -1**	**Day 1 (Baseline)**	**Day 7[b]**	**Day 14[b]**	**Day 28[b,c]**	**Day 42[b,d]**
Visit ID (for Sponsor use only)	**1**		**2**	**3**	**4**	**5[c]**	**6**
Study Procedures							
Patient Assessment of Constipation Quality of Life Scale			X		X	X	
Patient Assessment of Constipation Symptoms Scale			X		X	X	
EQ-5D			X		X	X	
Work Productivity and Impairment Scale			X		X	X	
Opioid-Related Symptom Distress Scale			X		X	X	

CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQoL Questionnaire; PK = pharmacokinetic; OOWS = Objective Opioid Withdrawal Scale; SOWS = Subjective Opioid Withdrawal Scale;.

a. The screening period had a + 3-day visit window to allow for weekends and slight variations in subject schedules. The minimum period was 14 days.
b. Every effort was made to schedule visits on the designated study days; however, after Baseline, office visits had a ± 3-day visit window to allow for weekends and slight variations in subject schedules.
c. For subjects who discontinued from the study early, the procedures scheduled for Study Day 28 were obtained on the last day the subjects took a full dose of test article or as soon as possible thereafter. The visit ID for the Early Termination Visit was 98.
d. All subjects were required to have a follow-up evaluation.
e. Single-blind, placebo run-in test article was dispensed at Visit 1 (Study Day –14). Double-blind test article was dispensed at subsequent visits.
f. Eligible subjects took their dose of double-blind test article during the office visit after all required procedures had been performed.
g. Trough PK sample was collected before test article administration.
h. An additional peak PK sample was collected at either 3- to < 6 hours, 6- to < 9 hours, or 9- to 12 hours after dose administration for willing subjects. The time interval was based on assigned randomization number.
i. Supine and standing blood pressure and pulse rate.
j. Subjects could be fasting or non-fasting. Specimens for hematology, blood chemistry, and urinalysis were obtained.
k. For women only. At Baseline, a urine pregnancy determination was performed. At all other specified visits, a serum pregnancy determination was performed.
l. A single 12-lead electrocardiogram recording was performed.
m. Collected from the signing of the informed consent form to 14 days after the last dose of test article.
n. Subjects completed the diary information daily.
o. Included time of bowel movement.
p. To be completed for each reported bowel movement. Information was not provided if the subject did not had a bowel movement. Number of bowel movements and time of the bowel movements were also reported.
q. Included type and time of medication.
r. Reported by subject on daily paper diary card. Included name, dosage, date, and time (for rescue opioid use for breakthrough pain only) of medication. Information recorded on CRF at visits indicated.

Number of Subjects (Planned and Analyzed): Approximately 210 to 420 subjects were planned for the double-blind portion of the study. In total, 242 subjects were randomly assigned to treatment and 236 received test article.

Diagnosis and Main Criteria for Inclusion: Outpatient men and women aged ≥18 years with OIBD and chronic non-malignant pain. Subjects taking oral, transdermal, intravenous, or subcutaneous opioids. Subjects willing to discontinue all pre-study laxative therapy and utilize only study permitted rescue laxatives.

Main Exclusion Criteria: Subjects with history of chronic constipation before the initiation of opioid therapy, other gastrointestinal (GI) disorders known to affect bowel transit or women who were pregnant, breast-feeding, or planned to become pregnant.

Study Treatment: Test article was provided as identical capsules in 10 mg, 50 mg or 150 mg strengths of MOA-728 and matching placebo for oral administration. Each daily dose consisted of 3 capsules. At the Baseline Visit, subjects were randomly assigned to 1 of the 6 groups (10 mg, 50 mg, 150 mg, 300 mg, and 450 mg of MOA-728 or placebo).

Subjects were instructed to take the test article as a single dose, once daily in the morning, except on days of office visits, and were also instructed not to eat within 2 hours before or after taking their dose. The double-blind treatment period was 28 days.

On days of office visits, subjects were instructed not to take the test article before the visit. The dose was administered during the visit, after blood samples were collected for the purpose of pharmacokinetic analyses.

Efficacy Endpoints:

Primary Endpoint: Change from Baseline in the number of spontaneous bowel movements (SBMs) per week during the double-blind treatment period.

Secondary Endpoints:

The time to first SBM for MOA-728 compared to placebo;

- The proportion of subjects with improvement in the signs and symptoms related to constipation, including abdominal pain and bloating, appetite, stool consistency, completeness, and straining;
- Change from Baseline in the number of quality spontaneous bowel movements (QSBMs) per week during the double-blind treatment period;
- Percentage of subjects with an increase of at least 1 complete (C)SBM per week during the double-blind treatment period relative to the baseline number;
- Percentage of subjects with an increase of at least 1 (C)SBM at Weeks 1, 2, 3, and 4 relative to the baseline number;

- Percentage of subjects with ≥3 (C)SBMs per week during the double-blind treatment period;
- percentage of subjects with ≥3 (C)SBMs at Weeks 1, 2, 3, and 4;
- Proportion of subjects who were able to achieve ≥3 (C)SBMs per week for 4 weeks;
- The time to achieving ≥3 (C)SBMs per week;
- Weekly average of scores on the Pain Intensity Scale;
- The change in the number of rescue laxative/enema doses taken during the double-blind treatment period relative to the baseline number.

Safety Evaluations: Safety was evaluated from reported symptoms and signs, AEs, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests.

Statistical Methods:

Modified Intent-to-Treat (mITT) Population: Defined as all randomized subjects who received at least 1 dose of double-blind test article. The mITT was the primary population for efficacy analysis and safety analysis.

Per-Protocol (PP) Population: Defined as a subset of the MITT population excluding subjects who had major protocol violations based on medical monitor judgment.

A statistical comparison among treatment groups was conducted using the Fisher exact test for the incidence of all AEs, treatment-emergent adverse events (TEAEs), potentially clinically important (PCI) laboratory test results and premature withdrawals during the study. A 1-way analysis of variance model with treatment group as a factor was used to compare groups for all continuous variables such as vital sign measurements and routine laboratory test parameters, except for nominal attributes (eg, sex), which were compared by the Fisher exact test.

The primary efficacy endpoint was analyzed using an analysis of covariance with treatment as a factor and baseline as a covariate. A Bayesian algorithm was used on the data of for the primary endpoint of SBMs and a secondary endpoint, quality SBMs (QSBMs, ie, SBM with stool quality other than diarrhea (Bristol score 1-5) to fit a dose-response model).

RESULTS

Subject Disposition and Demography: A total of 236 received at least 1 dose of test article and comprised the mITT population. A total of 205 subjects (86.9%) completed the study and 31 (13.1%) discontinued. The reasons for the subject's conclusion of participation in the study are summarized in Table 2.

Table 2. Summary of Reasons for Conclusion of Subject Participation, Modified Intent-to-Treat Population

Conclusion Status Reason	Overall p-Value	Treatment						Total N=236 n (%)
		MOA-728					Placebo N=44 n (%)	
		10 mg N=31 n (%)	50 mg N=36 n (%)	150 mg N=33 n (%)	300 mg N=45 n (%)	450 mg N=47 n (%)		
Total		31 (100)	36 (100)	33 (100)	45 (100)	47 (100)	44 (100)	236 (100)
Completed	0.064	26 (83.9)	33 (91.7)	32 (97.0)	41 (91.1)	35 (74.5)	38 (86.4)	205 (86.9)
Discontinued	0.064	5 (16.1)	3 (8.3)	1 (3.0)	4 (8.9)	12 (25.5)	6 (13.6)	31 (13.1)
Adverse event	0.931	1 (3.2)	1 (2.8)	0	1 (2.2)	1 (2.1)	2 (4.5)	6 (2.5)
Failed to return	0.754	1 (3.2)	1 (2.8)	0	0	2 (4.3)	1 (2.3)	5 (2.1)
Other	0.094	3 (9.7)	0	0	2 (4.4)	2 (4.3)	0	7 (3.0)
Protocol violation	0.718	0	1 (2.8)	1 (3.0)	1 (2.2)	3 (6.4)	3 (6.8)	9 (3.8)
Subject request	0.009*	0	0	0	0	4 (8.5)	0	4 (1.7)

*Statistical significance at the 0.01 level.
Overall p-value: Fishers exact test p-value (2-tail).
MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects meeting specified criteria.

Of these 236 subjects, 139 (58.9%) were women and 97 (41.1%) were men with OIBD and chronic non-malignant pain, in the age range of 19 to 87 years. The treatment groups were well balanced with respect to demographic and baseline disease characteristics. Subject demographics are summarized in Table 3.

Table 3. Summary of Demographic and Baseline Characteristics, Modified Intent-to-Treat Population

Characteristics	Treatment						Total N=236
	MOA-728					Placebo N=44	
	10 mg N=31	50 mg N=36	150 mg N=33	300 mg N=45	450 mg N=47		
Age (years), n							
Mean	48.71	51.00	50.94	54.91	48.89	53.05	51.40
Standard deviation	10.02	10.55	12.01	13.70	11.55	10.90	11.71
Minimum	33.00	23.00	26.00	26.00	19.00	30.00	19.00
Maximum	79.00	78.00	78.00	87.00	76.00	77.00	87.00
Median	47.00	52.50	51.00	53.00	49.00	53.50	51.00
Sex, n (%)							
Male	12 (38.7)	13 (36.1)	13 (39.4)	20 (44.4)	20 (42.6)	19 (43.2)	97 (41.1)
Female	19 (61.3)	23 (63.9)	20 (60.6)	25 (55.6)	27 (57.4)	25 (56.8)	139 (58.9)

MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects with specified criteria.

Efficacy Results: The study was terminated because of lack of efficacy therefore limited results are available.

There were no statistically significant differences observed among the treatment groups in the primary endpoint or in the secondary endpoint of QSBM (Table 4).

Table 4. Summary of Weekly Number of SBMs and QSBMs by Treatment Group (mITT With Observed-Case Data)

Endpoint	Treatment	N	Raw	Raw Change	Adjusted Change	Difference in Adjusted change vs. Placebo	
			Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	p-Value
Weekly number of SBMs	Placebo	44	2.8(2.4)	1.7(2.1)	1.7(0.3)		
	MOA-728 10 mg	29	2.2(1.6)	1.1(1.5)	1.0(0.3)	-0.7(-1.5,0.2)	0.139
	MOA-728 50 mg	35	2.5(2.2)	1.1(2.2)	1.1(0.3)	-0.6(-1.4,0.2)	0.163
	MOA-728 150 mg	33	3.1(1.9)	1.3(1.7)	1.4(0.3)	-0.3(-1.1,0.6)	0.520
	MOA-728 300 mg	44	2.8(1.8)	1.6(1.7)	1.6(0.3)	-0.1(-0.8,0.7)	0.878
	MOA-728 450 mg	46	2.6(1.8)	1.5(1.7)	1.5(0.3)	-0.2(-1.0,0.5)	0.574
Weekly number of QSBMs	Placebo	44	2.5(1.9)	1.5(1.7)	1.4(0.3)		
	MOA-728 10 mg	29	2.1(1.5)	0.9(1.6)	0.9(0.3)	-0.5(-1.3,0.3)	0.213
	MOA-728 50 mg	35	2.3(2.1)	1.0(2.1)	1.0(0.3)	-0.4(-1.2,0.4)	0.285
	MOA-728 150 mg	33	2.8(1.8)	1.3(1.6)	1.4(0.3)	-0.0(-0.8,0.8)	0.970
	MOA-728 300 mg	44	2.5(1.7)	1.4(1.6)	1.3(0.3)	-0.1(-0.8,0.6)	0.794
	MOA-728 450 mg	46	2.5(1.7)	1.3(1.7)	1.3(0.3)	-0.1(-0.8,0.6)	0.766

p-Value vs. placebo group was based on ANCOVA Model change = baseline + treatment.
ANCOVA = analysis of covariance; CI = confidence interval; MOA-728 = methylnaltrexone; N = number of subjects; QSBMs = quality spontaneous bowel movements; SBMs = spontaneous bowel movements; SD = standard deviation; SE = standard error; vs = versus.

Safety Results: A total of 122 (51.7%) of the 236 subjects in the mITT population had at least 1 or more AEs. A total of 105 (44.5%) of 236 subjects in the mITT population had TEAEs. There was no significant difference observed among the treatment groups in the overall occurrence of TEAEs (p=0.225). The most frequently reported TEAEs were GI disorders, reported by 44 (18.6%) of the 236 subjects. A summary of TEAEs with a ≥5% cutoff reported during the study is summarized in Table 5.

Table 5. Number (%) of Subjects Reporting ≥5% Treatment-Emergent Adverse Events, Modified Intent-to-Treat Population

System Organ Class[a] Preferred Term	Treatment						Total N=236
	MOA-728					Placebo N=44	
	10 mg N=31	50 mg N=36	150 mg N=33	300 mg N=45	450 mg N=47		
Any adverse event	9 (29.0)	18 (50.0)	15 (45.5)	21 (46.7)	26 (55.3)	16 (36.4)	105(44.5)
Gastrointestinal disorders	2 (6.5)	6 (16.7)	10 (30.3)	10 (22.2)	8 (17.0)	8 (18.2)	44 (18.6)
Abdominal pain	1 (3.2)	4 (11.1)	1 (3.0)	0	1 (2.1)	2 (4.5)	9 (3.8)
Diarrhea	0	0	1 (3.0)	1 (2.2)	2 (4.3)	3 (6.8)	7 (3.0)
Flatulence	0	1 (2.8)	1 (3.0)	4 (8.9)	2 (4.3)	1 (2.3)	9 (3.8)
Nausea	0	2 (5.6)	5 (15.2)	2 (4.4)	1 (2.1)	1 (2.3)	11 (4.7)
General disorders and administration site conditions	0	1 (2.8)	3 (9.1)	5 (11.1)	1 (2.1)	0	10 (4.2)
Fatigue	0	0	2 (6.1)	2 (4.4)	0	0	4 (1.7)
Metabolism and nutrition disorders	0	0	4 (12.1)	2 (4.4)	3 (6.4)	1 (2.3)	10 (4.2)
Decreased appetite	0	0	2 (6.1)	1 (2.2)	0	0	3 (1.3)
Musculoskeletal and connective tissue Disorders	1 (3.2)	1 (2.8)	1 (3.0)	4 (8.9)	5 (10.6)	0	12 (5.1)
Back pain	0	0	0	0	3 (6.4)	0	3 (1.3)
Nervous system disorders	0	2 (5.6)	4 (12.1)	3 (6.7)	3 (6.4)	1 (2.3)	13 (5.5)
Dizziness	0	2 (5.6)	1 (3.0)	0	1 (2.1)	1 (2.3)	5 (2.1)
Vascular disorders	0	3 (8.3)	1 (3.0)	0	4 (8.5)	1 (2.3)	9 (3.8)
Orthostatic hypotension	0	2 (5.6)	0	0	1 (2.1)	1 (2.3)	4 (1.7)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
MOA-728 = methylnaltrexone; N = total number of subjects.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Data regarding treatment related AEs is not available.

Serious Adverse Events (SAEs): There was no significant difference among the treatment groups in the incidence of SAEs (p=0.167). Six (6, 2.5%) of 236 subjects had SAEs during the study, none of which were considered related to the study drug. One (1) subject (0.4%) each in the 10 mg and 150 mg treatment groups and 3 subjects (6.4%) in the 450 mg treatment group reported ≥1 SAEs. A summary of SAEs reported during the study is presented in Table 6.

Table 6. Number (%) of Subjects Reporting Serious Adverse Events Modified Intent-to-Treat Population

System Organ Class[a] Preferred Term	Treatment						Total N=236
	MOA-728					Placebo N=44	
	10 mg N=31	50 mg N=36	150 mg N=33	300 mg N=45	450 mg N=47		
Any adverse event	1 (3.2)	0	1 (3.0)	0	3 (6.4)[b]	0	5(2.1)[b]
Gastrointestinal disorders	1 (3.2)	0	0	0	0	0	1(0.4)
Pancreatitis acute	1 (3.2)	0	0	0	0	0	1(0.4)
Infections and infestations	0	0	0	0	1 (2.1)	0	1(0.4)
Cellulitis	0	0	0	0	1 (2.1)	0	1(0.4)
Injury, poisoning and procedural complications	0	0	1 (3.0)	0	1 (2.1)	0	2(0.8)
Accidental overdose	0	0	1 (3.0)	0	0	0	1(0.4)
Hip fracture	0	0	0	0	1 (2.1)	0	1(0.4)
Neoplasms, benign, malignant and unspecified (inclusive cysts and polyps)	0	0	0	0	1 (2.1)	0	1(0.4)
Basal cell carcinoma	0	0	0	0	1 (2.1)	0	1(0.4)
Nervous system disorders	0	0	1 (3.0)	0	0	0	1(0.4)
Convulsion	0	0	1 (3.0)	0	0	0	1(0.4)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities.
AEs = adverse events; MOA-728 = methylnaltrexone; N = total number of subjects; SAEs = serious adverse events.

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different AEs within the higher level category.

b. A data error for SAEs was found after the database was frozen. Mucosa associated lymphoid tissue lymphoma of left tricep was reported for 1 subject as an AE in the clinical database, but was discovered to be an SAE after the database was frozen. The database was not updated to include this SAE, hence the number of subjects with SAEs in the MOA-728 450 mg group was 4 (8.5%) of 47 subjects and total number of subjects with SAEs was 6 (2.5%) of 236 subjects

Discontinuations due to AEs: Six (6) subjects (2.5%) withdrew from the study because of the following AEs: alanine aminotransferase/ aspartate aminotransferase levels increased, cellulitis, tremor, abdominal pain, nausea, and urinary tract infection (1 subject for each event).

Deaths: No deaths were reported during the study.

Laboratory Evaluations: Overall, 100 (42.4%) subjects of the 236 subjects in the mITT population, had PCI laboratory values (p =0.023). The number of subjects with PCI blood chemistry lab results were significantly different among the treatment groups (p =0.037), however no relationship to treatment was noted. The number of subjects with PCI calcium lab results were significantly different among the treatment groups (5 of 236 subjects; p =0.017). All 5 subjects with PCI calcium levels were randomized to receive MOA-728; however, no relationship to dose was noted.

Vital Signs and ECG Findings: A total of 68 (28.8%) of 236 subjects in the mITT population showed PCI vital sign measurements, with no significant differences observed among the treatment groups of MOA-728. A total of 22 (9.3%) subjects in the mITT population had PCI ECG abnormalities (overall evaluation). All subjects who had a PCI ECG abnormality after receiving test article also had a PCI abnormality at Screening.

CONCLUSION: The results from this clinical study suggest that the drug MOA-728 was well tolerated at single doses up to 450 mg (oral formulation). No deaths occurred during the

study and 6 (2.5%) of the 236 subjects who participated in the study drug had SAEs, none of which were considered related to the study drug. None of the doses showed adequate efficacy and resulted in the termination of the study.