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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Relistor® / N-methylnaltrexone bromide

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00804141

PROTOCOL NO.: B2541003 (3200K1-3358-WW)

PROTOCOL TITLE: An Open-Label Study to Evaluate the Long-Term Safety of Subcutaneous MOA-728 for Treatment of Opioid-Induced Constipation in Subjects With Nonmalignant Pain

Study Center(s): A total of 120 centers took part in the study, including 94 in the United States, 17 in Canada, 4 in Korea, 2 in Colombia, 2 in Spain and 1 in Australia.

Study Initiation Date and Completion Date: 03 December 2008 to 20 September 2010

Phase of Development: Phase 3

Study Objective(s): The primary objective of the study was to evaluate the long term safety and tolerability of the subcutaneous (SC) formulation of MOA-728 in subjects with opioid induced constipation (OIC) who have nonmalignant pain.

The secondary objective of the study was to assess the long term efficacy of the SC formulation of MOA-728 in subjects with OIC who have nonmalignant pain.

METHODS

Study Design: This was a phase 3 multicenter, open-label study to evaluate the long term safety and tolerability of SC MOA-728 in subjects with OIC who have nonmalignant pain.

The subjects participated in the study for approximately 52 weeks, which consisted of a 2-week screening period, a 48-week period of open-label treatment, and a 2-week post-treatment follow-up period. During the open-label period, subjects were to administer MOA-728 12 mg SC once daily. Dosing could be adjusted to an as needed basis (PRN) with a minimum 1 dose per week and maximum 1 dose per day. Bowel movement (BM) information was collected daily via telephonic diary using an interactive voice response system (IVRS) and included assessments utilizing the Bristol Stool Form Scale, the Straining Scale, and the Sense of Complete Evacuation Scale.

Number of Subjects (Planned and Analyzed): The planned sample size was 1000 subjects. A total of 1673 subjects who signed an informed consent form (ICF) were screened at 120 investigational sites worldwide. Of these, 633 subjects were screen failures. The remaining 1040 subjects who met the inclusion/exclusion criteria were assigned to receive treatment and 1034 of these subjects received at least 1 dose of test article and were included in the all-subjects population used for efficacy and safety summaries. Of the 1034 subjects who received test article, 477 completed the study and were included in the completer population.

Diagnosis and Main Criteria for Inclusion: Subjects who met the following criteria at screening were eligible to participate: male or female subjects aged 18 years or older with a history of pain of at least 2 months duration before the screening visit due to a documented underlying nonmalignant condition. Subjects had to be taking oral, transdermal, intravenous, or SC opioids daily for at least 1 month, with anticipated continuing daily opioid therapy for the duration of the study. The subjects had to have a history of constipation due to opioid use during 1 month before the screening visit and had to have at least 1 BM in the week prior to the screening visit. Based on daily diary reporting, subjects had to satisfy 2 or more of the following criteria during the screening period to continue in the study:

a. Hard or lumpy stools for at least 25% of the BMs.

b. Straining during at least 25% of the BMs.

c. A sensation of incomplete evacuation after at least 25% of the BMs.

d. Use of manual maneuvers (eg, digital evacuation, support of pelvic floor) to facilitate BMs at least 25% of the time.

e. Fewer than 3 BMs per week.

Study Treatment: The test article was provided to all eligible subjects as MOA-728 SC injection in prefilled syringes to be injected once daily for 48 weeks. The syringes contained a single 12 mg dose in 0.6 mL (20 mg/mL). Dosing could have been adjusted to PRN with a minimum 1 dose per week and maximum 1 dose per day. Subjects who were unwilling to administer or unable to tolerate a minimum dose of once per week were discussed with the sponsor and were withdrawn if unable to maintain dosing at least once weekly. Each subject and/or designee received materials and training by study site staff on how to perform an SC injection using the prefilled syringes, including an institutional review board/independent ethics committee (IRB/IEC) approved instructional video for the injection.

Efficacy Evaluations: The efficacy assessments for this study included recording of daily subject diary information (including BM count, time of BM, Bristol Stool Form Scale, Straining Scale, and Sense of Complete Evacuation Scale) using an IVRS diary system via telephone beginning the day of the screening visit and continuing through the subject's final study visit.

Efficacy endpoints included: weekly BM rate, percentage of injections resulting in BM within 4 hours, average of BM Bristol Stool Scale, average of BM Straining Scale, and average percentage of BMs with a sensation of complete evacuation.

Safety Evaluations: Height, weight, and vital signs (supine and standing pulse rate and blood pressure (BP)) were taken at screening, day 1, weeks 4, 8, 12, 16, 24, 32, 40, 48 or early termination visit and follow-up. Comprehensive physical examinations and laboratory evaluations were assessed at screening, week 24, and week 48 or early termination visit. Pregnancy tests for all women and standard 12 lead electrocardiograms (ECG) were administered at screening and day 1. Adverse events (AEs) and prior/concomitant treatments and medications, including opioid use were recorded from the time the ICF had been signed (screening visit) to the time of the follow-up visit. The Pain Intensity Scale was assessed at day 1, weeks 4, 8, 12, 16, 24, 32, 40, and week 48 or early termination visit. The Objective Opioid Withdrawal Scale (OOWS) to measure clinician assessed symptoms of opioid withdrawal and the Subjective Opioid Withdrawal Scale (SOWS) to measure subject assessed symptoms of opioid withdrawal were completed before administration and approximately 1 hour after administration of the first dose of test article.

Statistical Methods: Safety and efficacy data were analyzed based on the all-subjects population which included all subjects who took at least 1 dose of test article. Efficacy analyses were also performed for the completer population which included subjects who completed the 48-week open-label study based on the open-label phase conclusion record.

Efficacy: For the percentage of injections resulting in BM within 4 hours, descriptive summary statistics were reported by month. For weekly BM rate, the average of BM Bristol Stool Scale, the average of BM Straining Scale, and the average percentage of BMs with a sensation of complete evacuation, descriptive summary statistics for these efficacy endpoints and their changes from baseline were reported by month.

Safety: The incidence of all AEs and treatment-emergent adverse events (TEAEs) were summarized. AEs were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and summaries of the number of subjects with events were provided. Reports summarized by severity and by relationship to test article were provided.

Listings and summary tables were produced for vital signs (weight and sitting and standing BP and pulse rate), laboratory evaluations (hematology, blood chemistry, and urinalysis), OOWS, SOWS, Pain Intensity Scale, and 12 lead ECGs. For laboratory data, basic summary statistics (eg, N, mean and standard deviation, median, minimum, maximum) were reported for continuous laboratory endpoints and their changes from baseline. The potentially clinically important (PCI) criteria were evaluated for laboratory data, vital signs and ECGs. The numbers and proportion of subjects with PCI observations/events were reported.

For average of daily oral morphine equivalent, summary statistics (eg, N, mean and standard deviation, median, minimum, maximum) were reported for the open-label treatment period and their changes from baseline. The endpoint of average of daily oral morphine equivalent was calculated as sum of total oral morphine equivalent in a data analysis interval (DAI)/number of days in the DAI.

RESULTS

Subject Disposition and Demography: A total of 1673 subjects who signed an ICF were screened at 120 investigational sites worldwide. Of these, 633 subjects were screen failures. The remaining 1040 subjects who met the inclusion/exclusion criteria were assigned to receive treatment and 1034 of these subjects received at least 1 dose of test article and were included in the all-subjects population used for efficacy and safety summaries. Six (6) subjects were assigned an open-label treatment number but not treated. Of the 1034 subjects who received test article, 477 completed the study and were included in the completer population. A summary of the subject disposition by analysis population is provided in Table 1.

Table 1 . Summary of Analysis Populations by Treatment: All Subjects

Population Group	Treatment MOA-728 12 mg QD	Total Subjects
Screened		1673
Screen failures		633
Assigned Treatment	1040	1040
Assigned But Not Treated	6	6
All-Subjects Population [a]	1034	1034
Completer Population [b]	477	477

QD = once daily.

a. The all-subjects population included all subjects who took at least 1 dose of test article.

b. The completer population included subjects who completed the 48-week open-label study based on the open-label phase conclusion record.

The all-subjects population consisted of more women (64.7%) than men (35.3%); the mean age was 51.67 years (Table 2). The majority of subjects were white (89.7%) and non-Hispanic/Latino (95.6%). As expected for a population with chronic pain and symptomatic OIC, the most commonly reported primary pain condition at study entry was back pain (53.8%). The mean duration of OIC among subjects was 341.37 weeks.

The median baseline dose of opioid medication was 120.0 mg/day, which is expressed as oral morphine equivalents.

Table 2 . Summary of Demographic and Baseline Characteristics : All-Subjects Population

Characteristic	Treatment	
	MOA-728 12mg QD (n = 1034)	Total (n = 1034)
Age (Years), N		
N	1034	1034
Mean	51.67	51.67
Standard Deviation	10.84	10.84
Minimum	23.00	23.00
Maximum	81.00	81.00
Median	52.00	52.00
Sex, N (%)		
Male	365 (35.3)	365 (35.3)
Female	669 (64.7)	669 (64.7)
Race, N (%)		
Asian	12 (1.2)	12 (1.2)
Black or African American	76 (7.4)	76 (7.4)
White	927 (89.7)	927 (89.7)
Other	19 (1.8)	19 (1.8)
Ethnic Origin, N (%)		
Hispanic or Latino	45 (4.4)	45 (4.4)
Non-Hispanic and Non-Latino	989 (95.6)	989 (95.6)
Primary Pain Condition, N (%)		
Back pain	556 (53.8)	556 (53.8)
Cervical/neck pain	67 (6.5)	67 (6.5)
Fibromyalgia syndrome	75 (7.3)	75 (7.3)
Neuropathic pain	51 (4.9)	51 (4.9)
Osteoarthritis	112 (10.8)	112 (10.8)
Rheumatoid Arthritis	22 (2.1)	22 (2.1)
Other	151 (14.6)	151 (14.6)
Baseline Morphine Equiv Dose (mg), N		
N	1034	1034
Mean	199.73	199.73
Standard Deviation	232.17	232.17
Minimum	1.20	1.20
Maximum	2196.00	2196.00
Median	120.00	120.00
Duration of Opioid-induced Bowel Dysfunction (weeks), N		
N	1034	1034
Mean	341.37	341.37
Standard Deviation	297.49	297.49
Minimum	4.90	4.90
Maximum	2032.70	2032.70
Median	262.90	262.90
Baseline Height (cm), N		
N	1034	1034
Mean	168.57	168.57
Standard Deviation	10.03	10.03
Minimum	141.00	141.00
Maximum	213.40	213.40
Median	167.60	167.60
Baseline Weight (kg), N		
N	1034	1034
Mean	88.53	88.53

Table 2 . Summary of Demographic and Baseline Characteristics : All-Subjects Population

Characteristic	Treatment	
	MOA-728 12mg QD (n = 1034)	Total (n = 1034)
Standard Deviation	24.80	24.80
Minimum	39.00	39.00
Maximum	225.70	225.70
Median	85.40	85.40

QD = once daily.

Efficacy Results: The summary of weekly BM rate, average percentage of BMs with a sensation of complete evacuation, average of BM Bristol Stool Scale and average of BM Straining Scale for the all-subjects population is presented in Table 3. Over the entire open-label period, 34.1% of injections resulted in BMs within 4 hours. Results were consistent during the monthly intervals of the open-label period.

The mean weekly BM rate at baseline was 3.9; the mean weekly BM rate for the all-subjects population during the open-label treatment period who had at least 10 days of BM data was 5.3, a mean change of 1.5 BMs per week. Mean increases in BMs from baseline were observed for all time points during the 48-week open-label period. Although the mean weekly BM rate at follow-up (4.3) was lower from that for the last month of the open-label period (5.2), it remained higher compared to the baseline rate.

The mean percentage of BMs with a sensation of complete evacuation increased from 27.6 at baseline to 55.0 for the entire open-label period, an increase of 27.3 percentage points. The mean change from baseline in the percentage of BMs with a sensation of complete evacuation was 22.6 at the first month (weeks 1-4) of the open-label period, 29.0 at the last month of the open-label period, and 23.2 at follow-up.

The Bristol Stool Form Scale rates the form of BMs based on a scale from 1 to 7, with type 1 BMs being separate hard lumps and type 7 BMs being watery with no solid pieces. The average BM Bristol Stool Scale increased from 2.5 at baseline to 3.6 for the entire open-label period, an increase of 1.1. The results were consistent for all time points including follow-up.

The Straining Scale rates the amount of straining for BMs on a scale from 0 to 4, with 0 equaling none and 4 equaling very severe. The average BM Straining Scale decreased from 2.3 at baseline to 1.5 for the entire open-label period, a change of -0.9. Similar decreases from baseline in BM Straining Scale were observed for all time points including follow-up.

The efficacy results of subjects in the completer population were similar to the all-subjects population.

Table 3 . Summary of Weekly BM Rate, Average Percentage of BMs with a Sensation of Complete Evacuation, Average of BM Bristol Stool Scale and Average of BM Straining Scale: All-Subjects Population

		Raw Value					Change from baseline					
DAI	Treatment	N	Mean	SD	Median	Min-Max	N	Mean	SD	Median	Min-Max	P-value [a]
Weekly BM Rate												
Baseline	MOA-728 12 mg	1034	3.9	2.8	3.2	0.0-32.5						
OL period	MOA-728 12 mg	923	5.3	2.4	5.1	0.5-19.6	923	1.5	2.3	1.4	-16.4-11.7	<.001
The last month	MOA-728 12 mg	903	5.2	2.7	4.9	0.0-36.1	903	1.3	2.8	1.2	-19.8-28.1	<.001
Follow-up	MOA-728 12 mg	529	4.3	2.5	3.9	0.0-14.9	529	0.5	2.7	0.4	-21.4-11.1	<.001
Average Percentage of BMs with a Sensation of Complete Evacuation												
Baseline	MOA-728 12 mg	1034	27.6	31.2	18.2	0.0-100.0						
OL Period	MOA-728 12 mg	998	55.0	32.9	59.8	0.0-100.0	998	27.3	32.6	23.5	-100.0-100.0	<.001
The last month	MOA-728 12 mg	994	56.6	36.2	61.5	0.0-100.0	994	29.0	36.5	25.0	-100.0-100.0	<.001
Follow-up	MOA-728 12 mg	755	50.6	39.0	50.0	0.0-100.0	755	23.2	38.3	15.9	-100.0-100.0	<.001
Average of BM Bristol Stool Scale												
Baseline	MOA-728 12 mg	1031	2.5	1.3	2.3	1.0-7.0						
OL period	MOA-728 12 mg	998	3.6	1.2	3.7	1.0-7.0	996	1.1	1.3	1.0	-4.2-5.5	<.001
The last month	MOA-728 12 mg	992	3.6	1.3	3.8	1.0-7.0	990	1.1	1.4	1.0	-3.8-6.0	<.001
Follow-up	MOA-728 12 mg	753	3.3	1.4	3.3	1.0-7.0	752	0.9	1.5	0.8	-4.5-6.0	<.001
Average of BM Straining Scale												
Baseline	MOA-728 12 mg	1031	2.3	0.8	2.3	0.0-4.0						
OL period	MOA-728 12 mg	998	1.5	0.7	1.4	0.0-4.0	996	-0.9	0.9	-0.8	-3.9-1.9	<.001
The last month	MOA-728 12 mg	992	1.5	0.9	1.4	0.0-4.0	990	-0.9	1.0	-0.8	-4.0-2.7	<.001
Follow-up	MOA-728 12 mg	753	1.7	0.9	1.7	0.0-4.0	752	-0.6	1.0	-0.6	-3.9-3.0	<.001

BM = bowel movement; DAI = data analysis interval; OL = open label; SD = standard deviation.

a. P-value for within-group comparison based on paired t-test.

Safety Results: TEAEs were reported in 817 (79.0%) subjects (Table 4). The most frequently reported system organ class of TEAEs was gastrointestinal disorders (498 subjects, 48.2%). The most frequently reported TEAEs in the gastrointestinal disorders system organ class were abdominal pain (248 subjects, 24.0%), diarrhoea (170 subjects, 16.4%), and nausea (156 subjects, 15.1%). Other commonly reported system organ classes of TEAEs were infections and infestations (351 subjects, 33.9%), general disorders and administration site conditions (230 subjects, 22.2%), musculoskeletal and connective tissue disorders (206 subjects, 19.9%), and nervous system disorders (190 subjects, 18.4%). In addition, hyperhidrosis was also reported in 92 (8.9%) subjects.

Table 4 . Number (%) of Subjects Reporting Percentages ≥5% Treatment-Emergent Adverse Events: All-Subjects Population

	Treatment	
System Organ Class [a] **Preferred Term**	**MOA-728 12mg QD n=1034**	**Total n=1034**
Any Adverse Event	817 (79.0)	817 (79.0)
Gastrointestinal disorders	498 (48.2)	498 (48.2)
Abdominal pain	248 (24.0)	248 (24.0)
Abdominal pain upper	69 (6.7)	69 (6.7)
Diarrhoea	170 (16.4)	170 (16.4)
Flatulence	57 (5.5)	57 (5.5)
Nausea	156 (15.1)	156 (15.1)
Vomiting	74 (7.2)	74 (7.2)
General disorders and administration site conditions	230 (22.2)	230 (22.2)
Infections and infestations	351 (33.9)	351 (33.9)
Influenza	64 (6.2)	64 (6.2)
Sinusitis	55 (5.3)	55 (5.3)
Upper respiratory tract infection	60 (5.8)	60 (5.8)
Injury, poisoning and procedural complications	138 (13.3)	138 (13.3)
Investigations	107 (10.3)	107 (10.3)
Metabolism and nutrition disorders	67 (6.5)	67 (6.5)
Musculoskeletal and connective tissue disorders	206 (19.9)	206 (19.9)
Back pain	66 (6.4)	66 (6.4)
Nervous system disorders	190 (18.4)	190 (18.4)
Dizziness	52 (5.0)	52 (5.0)
Headache	58 (5.6)	58 (5.6)
Psychiatric disorders	111 (10.7)	111 (10.7)
Respiratory, thoracic and mediastinal disorders	117 (11.3)	117 (11.3)
Skin and subcutaneous tissue disorders	166 (16.1)	166 (16.1)
Hyperhidrosis	92 (8.9)	92 (8.9)
Vascular disorders	110 (10.6)	110 (10.6)

QD = once daily.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

One hundred and fifty seven (157, 15.2%) subjects withdrew from the study because of AEs (Table 5). The most common AEs resulting in withdrawal from the study were abdominal pain (49 subjects, 4.7%), nausea (26 subjects, 2.5%), and diarrhoea (24 subjects, 2.3%).

Table 5 . Number (%) of Subjects Reporting Adverse Events Causing Withdrawal from the Study: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment	
	MOA-728 12mg QD n=1034	Total n=1034
Any Adverse Event	157 (15.2)	157 (15.2)
Cardiac disorders	6 (0.6)	6 (0.6)
Angina pectoris	2 (0.2)	2 (0.2)
Angina unstable	1 (0.1)	1 (0.1)
Atrioventricular block second degree	1 (0.1)	1 (0.1)
Palpitations	2 (0.2)	2 (0.2)
Ventricular extrasystoles	1 (0.1)	1 (0.1)
Eye disorders	4 (0.4)	4 (0.4)
Choroiditis	1 (0.1)	1 (0.1)
Lacrimation increased	1 (0.1)	1 (0.1)
Ulcerative keratitis	1 (0.1)	1 (0.1)
Vision blurred	1 (0.1)	1 (0.1)
Gastrointestinal disorders	84 (8.1)	84 (8.1)
Abdominal distension	1 (0.1)	1 (0.1)
Abdominal pain	49 (4.7)	49 (4.7)
Abdominal pain lower	2 (0.2)	2 (0.2)
Abdominal pain upper	8 (0.8)	8 (0.8)
Abdominal rigidity	1 (0.1)	1 (0.1)
Colitis	1 (0.1)	1 (0.1)
Constipation	2 (0.2)	2 (0.2)
Diarrhoea	24 (2.3)	24 (2.3)
Dyspepsia	1 (0.1)	1 (0.1)
Gastrointestinal sounds abnormal	1 (0.1)	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)	1 (0.1)
Intestinal obstruction	1 (0.1)	1 (0.1)
Lower gastrointestinal haemorrhage	1 (0.1)	1 (0.1)
Nausea	26 (2.5)	26 (2.5)
Small intestinal obstruction	1 (0.1)	1 (0.1)
Vomiting	16 (1.5)	16 (1.5)
General disorders and administration site conditions	28 (2.7)	28 (2.7)
Asthenia	3 (0.3)	3 (0.3)
Chest discomfort	3 (0.3)	3 (0.3)
Chest pain	1 (0.1)	1 (0.1)
Chills	4 (0.4)	4 (0.4)
Drug withdrawal syndrome	2 (0.2)	2 (0.2)
Fatigue	3 (0.3)	3 (0.3)
Feeling abnormal	1 (0.1)	1 (0.1)
Feeling of body temperature change	2 (0.2)	2 (0.2)
Injection site erythema	1 (0.1)	1 (0.1)
Injection site inflammation	1 (0.1)	1 (0.1)
Injection site pain	2 (0.2)	2 (0.2)
Injection site pruritus	2 (0.2)	2 (0.2)
Injection site rash	1 (0.1)	1 (0.1)
Injection site reaction	1 (0.1)	1 (0.1)
Malaise	1 (0.1)	1 (0.1)
Non-cardiac chest pain	1 (0.1)	1 (0.1)
Pain	1 (0.1)	1 (0.1)
Pyrexia	1 (0.1)	1 (0.1)
Temperature intolerance	1 (0.1)	1 (0.1)

Table 5 . Number (%) of Subjects Reporting Adverse Events Causing Withdrawal from the Study: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment MOA-728 12mg QD n=1034	Total n=1034
Thirst	1 (0.1)	1 (0.1)
Hepatobiliary disorders	2 (0.2)	2 (0.2)
Cholecystitis	1 (0.1)	1 (0.1)
Cholecystitis acute	1 (0.1)	1 (0.1)
Cholelithiasis	1 (0.1)	1 (0.1)
Immune system disorders	1 (0.1)	1 (0.1)
Polyarteritis nodosa	1 (0.1)	1 (0.1)
Infections and infestations	3 (0.3)	3 (0.3)
Bronchopneumonia	1 (0.1)	1 (0.1)
Influenza	1 (0.1)	1 (0.1)
Pneumonia	2 (0.2)	2 (0.2)
Injury, poisoning and procedural complications	4 (0.4)	4 (0.4)
Contusion	1 (0.1)	1 (0.1)
Intentional overdose	1 (0.1)	1 (0.1)
Lower limb fracture	1 (0.1)	1 (0.1)
Meniscus lesion	1 (0.1)	1 (0.1)
Investigations	11 (1.1)	11 (1.1)
Activated partial thromboplastin time prolonged	1 (0.1)	1 (0.1)
Alanine aminotransferase increased	1 (0.1)	1 (0.1)
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)
Blood pressure increased	1 (0.1)	1 (0.1)
Electrocardiogram PR prolongation	1 (0.1)	1 (0.1)
Electrocardiogram QT prolonged	5 (0.5)	5 (0.5)
Heart rate decreased	2 (0.2)	2 (0.2)
International normalised ratio increased	1 (0.1)	1 (0.1)
Prothrombin time prolonged	1 (0.1)	1 (0.1)
Weight increased	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders	9 (0.9)	9 (0.9)
Arthralgia	1 (0.1)	1 (0.1)
Back pain	3 (0.3)	3 (0.3)
Muscle twitching	2 (0.2)	2 (0.2)
Myalgia	1 (0.1)	1 (0.1)
Pain in extremity	1 (0.1)	1 (0.1)
Sensation of heaviness	1 (0.1)	1 (0.1)
Spinal column stenosis	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	1 (0.1)
Breast cancer	1 (0.1)	1 (0.1)
Nervous system disorders	17 (1.6)	17 (1.6)
Ageusia	1 (0.1)	1 (0.1)
Dizziness	6 (0.6)	6 (0.6)
Headache	6 (0.6)	6 (0.6)
Migraine	1 (0.1)	1 (0.1)
Syringomyelia	1 (0.1)	1 (0.1)
Tremor	3 (0.3)	3 (0.3)
Pregnancy, puerperium and perinatal conditions	3 (0.3)	3 (0.3)
Pregnancy	3 (0.3)	3 (0.3)
Psychiatric disorders	13 (1.3)	13 (1.3)
Alcohol abuse	1 (0.1)	1 (0.1)
Anxiety	3 (0.3)	3 (0.3)

Table 5 . Number (%) of Subjects Reporting Adverse Events Causing Withdrawal from the Study: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment MOA-728 12mg QD n=1034	Total n=1034
Claustrophobia	1 (0.1)	1 (0.1)
Confusional state	1 (0.1)	1 (0.1)
Depersonalisation	1 (0.1)	1 (0.1)
Depression	4 (0.4)	4 (0.4)
Euphoric mood	1 (0.1)	1 (0.1)
Insomnia	1 (0.1)	1 (0.1)
Major depression	1 (0.1)	1 (0.1)
Restlessness	1 (0.1)	1 (0.1)
Renal and urinary disorders	4 (0.4)	4 (0.4)
Micturition urgency	1 (0.1)	1 (0.1)
Nephrolithiasis	1 (0.1)	1 (0.1)
Urinary incontinence	1 (0.1)	1 (0.1)
Urinary retention	2 (0.2)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	9 (0.9)	9 (0.9)
Asthma	1 (0.1)	1 (0.1)
Bronchial hyperreactivity	1 (0.1)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	1 (0.1)
Dyspnoea	3 (0.3)	3 (0.3)
Dyspnoea exertional	1 (0.1)	1 (0.1)
Respiratory distress	1 (0.1)	1 (0.1)
Rhinorrhoea	2 (0.2)	2 (0.2)
Yawning	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	20 (1.9)	20 (1.9)
Cold sweat	2 (0.2)	2 (0.2)
Erythema	1 (0.1)	1 (0.1)
Hyperhidrosis	16 (1.5)	16 (1.5)
Night sweats	1 (0.1)	1 (0.1)
Piloerection	1 (0.1)	1 (0.1)
Vascular disorders	10 (1.0)	10 (1.0)
Hot flush	6 (0.6)	6 (0.6)
Hypotension	3 (0.3)	3 (0.3)
Peripheral vascular disorder	1 (0.1)	1 (0.1)

Abbreviations: QD = once daily.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

Four (4) subjects (0.4%) died during this study. One (1) subject died during the open-label period. This subject had a treatment-emergent SAE of cerebrovasuclar accident considered unrelated to treatment that resulted in death 211 days after start of treatment. The other 3 subjects died during the follow-up period. One subject had an SAE of cardiac arrest considered unrelated to treatment that resulted in death 63 days after start of treatment (6 days after the last dosing date). One subject had an SAE of sudden death considered unrelated to treatment 257 days after start of treatment (7 days after the last dosing date). One subject had an SAE of myocardial infarction considered unrelated to treatment that resulted in death 278 days after start of treatment (after the early termination visit).

One hundred and four (104, 10.1%) subjects in the all-subjects population reported SAEs during this study (Table 6). SAEs reported by more than 2 subjects were pneumonia (8 subjects, 0.8%), back pain (5 subjects, 0.5%), myocardial infarction (4 subjects, 0.4%), abdominal pain (4 subjects, 0.4%), hypoaesthesia (4 subjects, 0.4%), asthma (4 subjects, 0.4%), chronic obstructive pulmonary disease (4 subjects, 0.4%), diarrhoea (4 subjects, 0.4%), non-cardiac chest pain, (4 subjects, 0.4%), angina pectoris (3 subjects, 0.3%), dehydration (3 subjects, 0.3%), and nausea (3 subjects, 0.3%). In addition, 3 subjects became pregnant during the study.

SAEs assessed by the investigator as related to test article were reported in 4 subjects. These included abdominal pain lower, hypotension, and depression each reported in 1 subject and myocardial infarction and hypertension reported in the same subject.

Table 6 . Number (%) of Subjects Reporting Serious Adverse Events: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment	
	MOA-728 12mg QD n=1034	Total n=1034
Any Adverse Event	104 (10.1)	104 (10.1)
Blood and lymphatic system disorders	2 (0.2)	2 (0.2)
Leukocytosis	1 (0.1)	1 (0.1)
Lymphadenopathy	1 (0.1)	1 (0.1)
Cardiac disorders	10 (1.0)	10 (1.0)
Angina pectoris	3 (0.3)	3 (0.3)
Cardiac arrest	1 (0.1)	1 (0.1)
Cardiac failure congestive	1 (0.1)	1 (0.1)
Coronary artery disease	2 (0.2)	2 (0.2)
Myocardial infarction	4 (0.4)	4 (0.4)
Prinzmetal angina	1 (0.1)	1 (0.1)
Eye disorders	3 (0.3)	3 (0.3)
Choroiditis	1 (0.1)	1 (0.1)
Ulcerative keratitis	1 (0.1)	1 (0.1)
Vision blurred	1 (0.1)	1 (0.1)
Gastrointestinal disorders	18 (1.7)	18 (1.7)
Abdominal pain	4 (0.4)	4 (0.4)
Abdominal pain lower	1 (0.1)	1 (0.1)
Abdominal pain upper	1 (0.1)	1 (0.1)
Colitis	2 (0.2)	2 (0.2)
Diarrhoea	4 (0.4)	4 (0.4)
Faecal incontinence	1 (0.1)	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)	1 (0.1)
Haematochezia	1 (0.1)	1 (0.1)
Intestinal obstruction	2 (0.2)	2 (0.2)
Localised intraabdominal fluid collection	1 (0.1)	1 (0.1)
Lower gastrointestinal haemorrhage	1 (0.1)	1 (0.1)
Lumbar hernia	1 (0.1)	1 (0.1)
Nausea	3 (0.3)	3 (0.3)
Oesophageal achalasia	1 (0.1)	1 (0.1)
Oesophageal dilatation	1 (0.1)	1 (0.1)
Pancreatitis	1 (0.1)	1 (0.1)
Pancreatitis acute	1 (0.1)	1 (0.1)
Small intestinal obstruction	2 (0.2)	2 (0.2)
Vomiting	2 (0.2)	2 (0.2)
General disorders and administration site conditions	9 (0.9)	9 (0.9)
Abasia	1 (0.1)	1 (0.1)
Asthenia	1 (0.1)	1 (0.1)
Chills	1 (0.1)	1 (0.1)
Device dislocation	1 (0.1)	1 (0.1)
Fatigue	1 (0.1)	1 (0.1)
Non-cardiac chest pain	4 (0.4)	4 (0.4)
Oedema peripheral	1 (0.1)	1 (0.1)
Pain	1 (0.1)	1 (0.1)
Sudden death	1 (0.1)	1 (0.1)
Hepatobiliary disorders	4 (0.4)	4 (0.4)
Cholecystitis	1 (0.1)	1 (0.1)
Cholecystitis acute	1 (0.1)	1 (0.1)
Cholelithiasis	1 (0.1)	1 (0.1)

Table 6 . Number (%) of Subjects Reporting Serious Adverse Events: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment MOA-728 12mg QD n=1034	Total n=1034
Gallbladder disorder	1 (0.1)	1 (0.1)
Jaundice	1 (0.1)	1 (0.1)
Immune system disorders	1 (0.1)	1 (0.1)
Polyarteritis nodosa	1 (0.1)	1 (0.1)
Infections and infestations	24 (2.3)	24 (2.3)
Appendicitis	1 (0.1)	1 (0.1)
Bronchitis	1 (0.1)	1 (0.1)
Bronchopneumonia	2 (0.2)	2 (0.2)
Cellulitis	2 (0.2)	2 (0.2)
Device related infection	1 (0.1)	1 (0.1)
Diverticulitis	1 (0.1)	1 (0.1)
Gastroenteritis	2 (0.2)	2 (0.2)
Gastroenteritis viral	1 (0.1)	1 (0.1)
Lower respiratory tract infection	1 (0.1)	1 (0.1)
Perihepatic abscess	1 (0.1)	1 (0.1)
Pneumonia	8 (0.8)	8 (0.8)
Pyelonephritis	1 (0.1)	1 (0.1)
Sepsis	1 (0.1)	1 (0.1)
Septic shock	1 (0.1)	1 (0.1)
Staphylococcal skin infection	1 (0.1)	1 (0.1)
Upper respiratory tract infection	1 (0.1)	1 (0.1)
Urinary tract infection	1 (0.1)	1 (0.1)
Wound infection staphylococcal	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	10 (1.0)	10 (1.0)
Accidental overdose	1 (0.1)	1 (0.1)
Fibula fracture	1 (0.1)	1 (0.1)
In-stent coronary artery restenosis	1 (0.1)	1 (0.1)
Intentional overdose	1 (0.1)	1 (0.1)
Lower limb fracture	1 (0.1)	1 (0.1)
Multiple fractures	1 (0.1)	1 (0.1)
Overdose	1 (0.1)	1 (0.1)
Post procedural bile leak	1 (0.1)	1 (0.1)
Post procedural haemorrhage	1 (0.1)	1 (0.1)
Road traffic accident	1 (0.1)	1 (0.1)
Spinal compression fracture	1 (0.1)	1 (0.1)
Traumatic liver injury	1 (0.1)	1 (0.1)
Investigations	2 (0.2)	2 (0.2)
Blood potassium decreased	1 (0.1)	1 (0.1)
Nuclear magnetic resonance imaging abnormal	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders	4 (0.4)	4 (0.4)
Decreased appetite	1 (0.1)	1 (0.1)
Dehydration	3 (0.3)	3 (0.3)
Hyperkalaemia	1 (0.1)	1 (0.1)
Hypokalaemia	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders	13 (1.3)	13 (1.3)
Arthralgia	1 (0.1)	1 (0.1)
Back pain	5 (0.5)	5 (0.5)
Intervertebral disc protrusion	1 (0.1)	1 (0.1)
Muscular weakness	1 (0.1)	1 (0.1)

Table 6 . Number (%) of Subjects Reporting Serious Adverse Events: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment MOA-728 12mg QD n=1034	Total n=1034
Musculoskeletal pain	2 (0.2)	2 (0.2)
Neck pain	1 (0.1)	1 (0.1)
Scoliosis	1 (0.1)	1 (0.1)
Spinal column stenosis	1 (0.1)	1 (0.1)
Spinal osteoarthritis	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	2 (0.2)
Breast cancer	1 (0.1)	1 (0.1)
Thyroid neoplasm	1 (0.1)	1 (0.1)
Nervous system disorders	13 (1.3)	13 (1.3)
Cerebrovascular accident	1 (0.1)	1 (0.1)
Convulsion	1 (0.1)	1 (0.1)
Dizziness	1 (0.1)	1 (0.1)
Dysarthria	1 (0.1)	1 (0.1)
Head discomfort	1 (0.1)	1 (0.1)
Hypoaesthesia	4 (0.4)	4 (0.4)
Migraine	1 (0.1)	1 (0.1)
Nerve compression	1 (0.1)	1 (0.1)
Neuralgia	2 (0.2)	2 (0.2)
Radiculopathy	1 (0.1)	1 (0.1)
Syncope	1 (0.1)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	3 (0.3)	3 (0.3)
Abortion spontaneous	1 (0.1)	1 (0.1)
Pregnancy	3 (0.3)	3 (0.3)
Psychiatric disorders	8 (0.8)	8 (0.8)
Alcohol abuse	1 (0.1)	1 (0.1)
Depression	2 (0.2)	2 (0.2)
Intentional drug misuse	1 (0.1)	1 (0.1)
Major depression	2 (0.2)	2 (0.2)
Mental status changes	1 (0.1)	1 (0.1)
Suicidal ideation	1 (0.1)	1 (0.1)
Renal and urinary disorders	2 (0.2)	2 (0.2)
Renal failure	2 (0.2)	2 (0.2)
Renal failure acute	1 (0.1)	1 (0.1)
Reproductive system and breast disorders	1 (0.1)	1 (0.1)
Dysfunctional uterine bleeding	1 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	13 (1.3)	13 (1.3)
Acute respiratory failure	1 (0.1)	1 (0.1)
Asthma	4 (0.4)	4 (0.4)
Atelectasis	1 (0.1)	1 (0.1)
Bronchial hyperreactivity	1 (0.1)	1 (0.1)
Chronic obstructive pulmonary disease	4 (0.4)	4 (0.4)
Dyspnoea	2 (0.2)	2 (0.2)
Pleural effusion	1 (0.1)	1 (0.1)
Pulmonary embolism	1 (0.1)	1 (0.1)
Respiratory distress	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	1 (0.1)
Granuloma skin	1 (0.1)	1 (0.1)
Surgical and medical procedures	1 (0.1)	1 (0.1)
Shoulder arthroplasty	1 (0.1)	1 (0.1)

Table 6 . Number (%) of Subjects Reporting Serious Adverse Events: All-Subjects Population

System Organ Class [a] Preferred Term	Treatment	
	MOA-728 12mg QD n=1034	Total n=1034
Vascular disorders	4 (0.4)	4 (0.4)
Hypertension	2 (0.2)	2 (0.2)
Hypotension	2 (0.2)	2 (0.2)

QD = once daily.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

Other Observations Related to Safety: Potential opioid withdrawal was assessed using clinician assessed (OOWS) and subject assessed (SOWS) scales to measure symptoms of opioid withdrawal. The OOWS scale ranged from 1 to 13 and the SOWS scale ranged from 1 to 19. The OOWS scores with and without the item related to cramping were similar. The mean change in OOWS score from baseline to day 1 was 0.2 overall (including cramping item) and 0.1 without the cramping item and was not considered clinically meaningful (Table 7). The mean change in SOWS score from baseline to day 1 was -2.5 overall (including cramping item) and -2.8 without the cramping item. Review of the SOWS data generally showed no evidence of withdrawal.

Average pain ratings over 24 hours in each phase were recorded on a scale of 0 (no pain) to 10 (worst possible pain). There was little change in the mean or median pain scores over time. The average morphine equivalent use increased slightly on weeks 25-28 (11.5), weeks 33-36 (13.6), weeks 37-40 (25.4), weeks 41-44 (16.8), and weeks 45-48 (11.7). The mean change from baseline in average of daily oral morphine equivalent use throughout the entire open-label treatment period was 3.0 mg/day and the median daily morphine equivalent use was similar throughout the entire open-label treatment period. The changes in morphine equivalent use were not deemed clinically significant.

Table 7 . Summary of Objective Opioid Withdrawal Scale (OOWS), Subjective Opioid Withdrawal Scale (SOWS), Pain Intensity Scale and Average of Daily Opioid Morphine Equivalent: All-Subjects Population

			Raw Value					Change from baseline				
Endpoint	**DAI**	**Treatment**	**N**	**Mean**	**SD**	**Median**	**Min-Max**	**N**	**Mean**	**SD**	**Median**	**Min-Max**
OOWS	Baseline	MOA-728 12 mg	1028	0.4	1.0	0.0	0.0-7.0					
	Day 1	MOA-728 12 mg	1021	0.6	1.3	0.0	0.0-12.0	1020	0.2	1.1	0.0	-4.0-10.0
OOWS Score - Without Cramping Item	Baseline	MOA-728 12 mg	1028	0.4	0.9	0.0	0.0-6.0					
	Day 1	MOA-728 12 mg	1021	0.5	1.2	0.0	0.0-11.0	1020	0.1	0.9	0.0	-4.0-9.0
Total SOWS Score	Baseline	MOA-728 12 mg	1033	12.3	9.9	10.0	0.0-58.0					
	Day 1	MOA-728 12 mg	1008	9.7	9.3	7.0	0.0-56.0	1007	-2.5	7.1	-1.0	-33.0-44.0
Total SOWS Score - Without Cramping Item	Baseline	MOA-728 12 mg	1033	11.7	9.4	10.0	0.0-54.0					
	Day 1	MOA-728 12 mg	1008	8.8	8.7	6.0	0.0-53.0	1007	-2.8	6.6	-1.0	-33.0-40.0
Pain Intensity Scale	Baseline	MOA-728 12 mg	1029	6.1	1.9	6.0	0.0-10.0					
	Week 4	MOA-728 12 mg	898	6.0	2.0	6.0	0.0-10.0	894	-0.1	1.8	0.0	-8.0-10.0
	Week 8	MOA-728 12 mg	789	6.0	2.1	6.0	0.0-10.0	785	-0.0	2.0	0.0	-9.0-8.0
	Week 12	MOA-728 12 mg	733	6.1	2.1	6.0	0.0-10.0	729	0.1	1.9	0.0	-7.0-9.0
	Week 16	MOA-728 12 mg	689	6.1	2.2	6.0	0.0-10.0	685	0.0	2.0	0.0	-8.0-9.0
	Week 24	MOA-728 12 mg	626	6.1	2.2	6.0	0.0-10.0	623	0.0	2.0	0.0	-7.0-9.0
	Week 32	MOA-728 12 mg	582	6.1	2.1	6.0	0.0-10.0	579	0.0	2.0	0.0	-9.0-9.0
	Week 40	MOA-728 12 mg	521	6.1	2.1	6.0	0.0-10.0	518	0.0	2.0	0.0	-7.0-9.0
	Week 48	MOA-728 12 mg	435	6.1	2.1	6.0	0.0-10.0	432	0.0	2.1	0.0	-7.0-10.0
	Follow-Up	MOA-728 12 mg	286	6.2	2.2	7.0	0.0-10.0	285	0.1	2.0	0.0	-6.0-7.0
Average of Daily Opioid Morphine Equivalent	Baseline	MOA-728 12 mg	1034	199.7	232.2	120.0	1.2-2196.0					
	OL Period	MOA-728 12 mg	985	200.9	241.6	118.7	0.0-2203.3	985	3.0	102.1	0.0	-1070-1331.1
	Follow-Up	MOA-728 12 mg	873	202.9	253.2	116.5	0.0-2160.0	873	3.9	117.8	0.0	-962.4-1564.5

DAI = data analysis interval; OL = open label; OOWS = Objective Opioid Withdrawal Scale; SOWS = Subjective Opioid Withdrawal Scale SD = standard deviation.

CONCLUSIONS:

- The number of injections resulting in BMs within 4 hours, the weekly BM rate, the percentage of BMs with a sensation of complete evacuation, the BM Bristol Stool Form Scale, and the BM Straining Scale were summarized on the all-subjects population and the completer population. For the all-subjects population on average, 34.1% of injections resulted in BMs within 4 hours for the open-label period and results were consistent across 4-week intervals during the study. The mean number of BMs increased from baseline during the open-label period by 1.5 BMs. This increase in BMs was observed for all time points during the 48-week open-label treatment period. These results were sustained over the 48-week course of the study and consistent with those observed in previous studies with MOA-728 (ie, study 3200K1-3356 WW, the phase 3 placebo-controlled study of MOA-728 SC to treat OIC in patients with chronic non malignant pain) and support the previous data from study 3356 that showed that MOA-728 promptly and reliably induces laxation in patients with chronic pain and OIC.

- The mean percentage of BMs with a sensation of complete evacuation increased from baseline during the open-label period by 27.3 percentage points. This increase from baseline in BMs with sensation of complete evacuation was observed for all time points including follow-up.

- The average BM Bristol Stool Form Scale was higher in the open-label period compared to baseline, indicating BMs were of improved consistency during the open-label period compared to baseline. This increase from baseline in BM Bristol Stool Form Scale was observed for all time points including follow-up.

- The average BM Straining Scale was lower in the open-label period compared to baseline, indicating decreased straining and increased ease of passage of BMs in the open-label period compared to baseline. This decrease from baseline in BM Straining Scale was observed for all time points including follow-up.

- TEAEs were reported in 817 (79.0%) subjects. The most frequently reported system organ class of TEAEs was gastrointestinal disorders (498 subjects, 48.2%). The most frequently reported TEAEs in the gastrointestinal disorders system organ class were abdominal pain (248 subjects, 24.0%), diarrhoea (170 subjects, 16.4%), and nausea (156 subjects, 15.1%).

- Four (4) subjects (0.4%) died during this study. The deaths were considered unrelated to treatment. One hundred and four (104, 10.1%) subjects in the all-subjects population reported SAEs during this study. SAEs reported by more than 2 subjects were pneumonia (8 subjects, 0.8%), back pain (5 subjects, 0.5%), myocardial infarction (4 subjects, 0.4%), abdominal pain (4 subjects, 0.4%), hypoaesthesia (4 subjects, 0.4%), asthma (4 subjects, 0.4%), chronic obstructive pulmonary disease (4 subjects, 0.4%), diarrhoea (4 subjects, 0.4%), non-cardiac chest pain, (4 subjects, 0.4%), angina pectoris (3 subjects, 0.3%), dehydration (3 subjects, 0.3%), and nausea (3 subjects, 0.3%). SAEs assessed by the investigator as related to test article were reported in 4 subjects.

- One (1) subject had a life threatening TEAE of myocardial infarction considered related to treatment.

- One hundred and fifty seven (157, 15.2%) subjects withdrew from the study because of AEs. The most common AEs resulting in withdrawal from the study were abdominal pain (49 subjects, 4.7%), nausea (26 subjects, 2.5%), and diarrhoea (24 subjects, 2.3%).

- MOA-728 had no clinically relevant effect on laboratory parameters, vital sign measurements, or ECG findings in this population.

- A review of individual subject data generally showed scores reflective of no opioid withdrawal symptoms. There was little change in the mean or median pain scores over time. Treatment with MOA-728 did not result in increased opioid requirements or changes in the OOWS or SOWS. These data together do not suggest any occurrence of opioid withdrawal.

- In conclusion, SC MOA-728 12 mg is effective in treating OIC by inducing more frequent BMs, and by inducing BMs with a sensation of complete evacuation, that are easier to pass and involve less straining. SC MOA-728 12 mg was safe and well tolerated.

- The results of this study support the long term safety and tolerability of SC MOA-728 12 mg administered once daily or PRN for 48 weeks. The results further support the previously established efficacy in shorter term studies of SC MOA-728 in providing increased BMs and improved stool characteristics over 48 weeks in subjects with chronic nonmalignant pain and OIC.