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PROPRIETARY NAME / GENERIC NAME: Relistor® / Methylnaltrexone

PROTOCOL NO.: 3200L2-300-WW (B2541042)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Intravenous Methylnaltrexone (MOA-728) for the Treatment of Post-Operative Ileus

Study Centers: A total of 96 centers took part in the study and randomized subjects; 3 in Australia, 3 in China, 3 in Czech Republic, 4 in Germany, 1 in Hong Kong, 4 in Hungary, 7 in Italy, 2 in Korea Republic, 5 in Poland, 3 in Romania, 2 in Serbia and Montenegro, 5 in South Africa, 1 in Taiwan, and 53 in the United States.

Study Initiation and Final Completion Dates: 05 December 2006 to 20 November 2007.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To test the following hypothesis: In subjects who have undergone segmental colectomy, the time between the end of surgery and first bowel movement is significantly shorter with the MOA-728 regimen than the equivalent assessment using a placebo regimen.

Secondary Objectives:

1) To assess the safety of intravenous (IV) MOA-728 administered every 6 hours in these post-surgical subjects;

2) To assess the effects of IV MOA-728 on the time from the end of surgery to discharge eligibility and time to hospital discharge;

3) To examine clinically meaningful events for nausea or retching/vomiting at 24 hours as assessed by the opioid related symptom distress scale (SDS) instrument.

METHODS

Study Design: This was a double-blind, randomized, parallel-group, placebo-controlled Phase 3 study to evaluate the safety and efficacy of IV MOA-728 versus placebo in shortening the duration of post-operative ileus in subjects who have undergone segmental colectomy via open laparotomy. Subjects were randomly assigned to receive IV MOA-728

or placebo every 6 hours for a maximum of 10 days. Subjects participated in the study for approximately 6 weeks (Table 1). The study duration was approximately 13 months.

Table 1. Study Flowchart

Study Procedures	**Days -21 to 1**	**Day 1 to Day 10 (Day 1 was the First Dose of Test Article)**					**Follow-Up**	
Study Interval	**Screening**	**Active Phase**					**Follow-Up**	
Assessments	**Screening**	**Pre-Op**	**Post-Op**		**Double-Blind Treatment Period**	**End of Treatment**[a]	**Follow-up**[b] **Day 7**	**Follow-up**[b] **Day 15**
		Day of Surgery	**Post Surgery**	**Pre Test Article**	**Assessments While on Test Article**			
Informed consent	X							
Inclusion/exclusion criteria	X	X	X					
Demography	X							
Medical history/surgical history/current medical conditions	X							
Physical examination	X					X	X	
Vital signs[c]	X	X	X	X	X	X	X	
Laboratory tests[d]	X					X	X	
Pregnancy test[e]	X[e]	X[e]						
ECG[f]	X			X	X[f]	X		
Randomization			X					
IV PCA administration[g]			X	X	X			
Clinical assessments[h]					X			
Test article IV administration[i]					X			
Surgical treatment assessment[j]			X					
Prior & concomitant medications	X	X		X	X	X	X	
Adverse events[k]	X	X	X	X	X	X	X	X
Subject global satisfaction with treatment						X		
Subject abdominal pain VAS[l]				X	X	X		
EQ-5D General Health Scale[m]	X				X[m]	X		
Opioid-Related SDS[n]					X[n]	X		

Table 1. Study Flowchart

Study Procedures	Days -21 to 1	Day 1 to Day 10 (Day 1 was the First Dose of Test Article)					Follow-Up	
Study Interval	Screening	Active Phase					Follow-Up	
Assessments	Screening	Pre-Op	Post-Op		Double-Blind Treatment Period	End of Treatment[a]	Follow-up[b] Day 7	Follow-up[b] Day 15
		Day of Surgery	Post Surgery	Pre Test Article	Assessments While on Test Article			

BP = blood pressure; ECG = electrocardiogram; EQ-5D = Euro Quality of Life (QOL) Questionnaire; IV = intravenous; LFT = liver function test; NG = nasogastric; OG = orogastric; PCA = patient-controlled analgesia; Pre-op = pre-operative; Post-op = post-operative; SDS = Symptom Distress Scale; VAS = visual analog scale.

a. End of Treatment assessment was conducted when a subject was discharged from the hospital, after 10 days of treatment have elapsed, or the subject had been withdrawn or terminated early for any reason from the study.
b. The subject had a safety follow up study visit approximately 7 days ±3 days after the last dose of test article; the site contacted the subject via telephone 15 days +3 days following their last dose of test article.
c. Vital signs (body temperature, pulse, BP, respiration) were taken at Screening, day of surgery, immediately prior to test article administration and at the end of test article administration for the first dose of test article on Days 1, 2, and 3, once daily during double-blind treatment after Day 3, and End of Treatment.
d. If more than 1 lab panel was taken during the day of assessment, the last full panel that was drawn should be recorded.
e. A serum pregnancy test was required at time of screening. A serum or urine pregnancy test was required within 72 hours of dosing.
f. On Day 1 (the first dose of test article), an ECG is performed prior to & following the completion of the initial test article infusion. On Day 2 and 3, an ECG is performed prior to and after the first or second test article infusion (depending on time of infusions). A 12-lead ECG is required for all time points.
g. Subjects should have access to IV opioid PCA for duration of study starting post-op and continuing until 24 hours after the subject's first bowel movement and was tolerating clear liquids, until the subject was discharged, for a maximum of 10 days without the subject tolerating at least clear liquids and having a bowel movement, or terminates early from the study if or any reason.
h. Clinical assessments were performed daily and included time of clear liquid tolerance, time of bowel movement, time of solid food tolerance, any insertion of NG, OG or urinary catheter for urinary retention. The time of Discharge (time when the discharge order is written) was recorded as part of these assessments.
i. Subjects received their first dose of test article within 90 minutes after the end of the surgery. Test article treatment was administered every 6 hours until: 24 hours after the subject had his or her first bowel movement and tolerated clear liquids, until the subject was discharged, for a maximum of 10 days without the subject tolerating at least clear liquids and having a bowel movement, or on early termination from the study for any reason.
j. Surgical treatment assessment data collected included all intraoperative medication, all opioid medications; the duration of the procedure and time of the end of procedure; and the volume of blood lost.
k. Adverse events were collected from the signing of the informed consent form through the 15 day follow-up visit.
l. The abdominal pain VAS was assessed prior to the initial dose of test article (if subject was awake and alert); taken after each dose of test article on Day 1; and then taken daily after the first or second dose (depending on timing of doses) of test article on each day thereafter.
m. EQ-5D was recorded at Screening, on Day 2 of test article, and at the End of Treatment.
n. SDS assessment was completed by the subject approximately 24 hours after the first dose (when the subject was awake) and then every day at approximately the same time the initial assessment was conducted.

Number of Subjects (Planned and Analyzed): Approximately 495 subjects were planned for the study (165 per treatment group). In total 678 subjects were enrolled (23 in Australia, 4 in China, 22 in Czech Republic, 35 in Germany, 2 in Hong Kong, 61 in Hungary, 40 in Italy, 96 in Korea Republic, 45 in Poland, 9 in Romania, 37 in Serbia and Montenegro, 47 in South Africa, 5 in Taiwan, 252 in United States), 533 subjects were randomized and analyzed, and 472 completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years scheduled for a segmental colectomy via open laparotomy with general anesthesia. Subjects with a history of inflammatory bowel disease were eligible as long as the disease was not currently active and all other criteria were met. Subjects meeting the American Society of Anesthesiologists physical status I, II or III.

Exclusion Criteria: Subjects scheduled for laparoscopic surgery for the segmental colectomy; with a recent history (<1 year prior to randomization) of abdominal radiation therapy; history of small bowel obstruction, known or suspected bowel adhesions (other than minor, clinically nonsignificant adhesions); subjects undergoing operations resulting in gastrointestinal ostomies, or who required use of post-operative nonsteroidal anti-inflammatory drugs.

Study Treatment: MOA-728 was supplied as lyophilized white powder for reconstitution with 50 mL of normal saline. Subjects were randomized to receive either IV MOA-728 (12 or 24 mg) or placebo (50 mL normal saline bags) intravenously, every 6 hours for a total of 4 doses in a 24 hour period and for a maximum of 10 days.

Efficacy Endpoints:

Primary Endpoint: Time to first bowel movement after the end of surgery (defined as the time when the last suture or staple is placed in the subject).

Secondary Endpoints:

- Time to discharge eligibility from end of surgery defined as toleration of solid food and at least one bowel movement;
- Time to discharge order written from the end of surgery;
- Clinically meaningful events for nausea and retching/vomiting at 24 hours as evaluated by the opioid related SDS.

Safety Evaluations: Safety assessments involved the monitoring and recording of all AEs and serious adverse events (SAEs), hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiogram (ECGs), and findings of physical examinations.

Statistical Methods: The modified intent-to-treat (MITT) population was defined as all randomized subjects who took at least 1 dose of test article. The MITT was the primary population for efficacy analysis.

The safety analysis population included all subjects who took at least 1 dose of test article.

For the primary endpoint the distribution of event times was estimated by the Kaplan-Meier product-limit method and compared between treatment groups by the log-rank test stratified by region. Two (2) comparisons were made: MOA-728 24 mg vs placebo and MOA-728 12 mg vs placebo. Treatment comparisons were made at the overall $\alpha = 0.05$ level (2-sided), using a closed sequential procedure. The placebo and MOA-728 24 mg treatment groups were compared first. If the comparison was significant ($p < 0 .05$) in favor of MOA-728, then the placebo and 12 mg MOA-728 dose groups were compared at the 0.05 level of significance.

Both the first key secondary endpoint, time to discharge eligibility, and the second key secondary endpoint, time to discharge order written, were analyzed using log-rank test stratified by region. The third key secondary endpoint, clinically meaningful events for nausea and retching/vomiting (as evaluated by the SDS) were tested every 24 hours using a Cochran-Mantel-Haenszel Chi-square test stratified by region.

The multiplicity among the primary endpoint and key secondary efficacy endpoints were controlled using a closed sequential procedure. If a significant difference was detected for the MOA-728 24 mg dose or both doses of MOA-728 for the primary endpoint, then the closed sequential procedure were applied to that dose group(s) for the key secondary efficacy endpoints as follows. The first key secondary endpoint was tested for that dose groups(s) vs placebo at the $\alpha = 0.05$ level of significance using the closed sequential procedure. The MOA-728 24 mg dose vs placebo was always tested first. If 1 or both MOA-728 dose groups were significant on the first key secondary endpoint, then the second key secondary endpoint was tested at the 0.05 level to compare that dose to placebo at the $\alpha = 0.05$ level of significance using the closed sequential procedure. If 1 or both MOA-728 dose groups were significant on the second key secondary endpoint, then the third key secondary endpoint was tested at the 0.05 level to compare that dose to placebo at the $\alpha = 0.05$ level of significance using the closed sequential procedure.

All time-to-event endpoints were analyzed using log-rank test stratified by region. Continuous variables were analyzed by analysis of variance. Categorical variables were tested using a Cochran-Mantel-Haenszel Chi-square test stratified by region or Fisher's exact test in case of small cell frequencies. These endpoints were evaluated at the $\alpha = 0.05$ level of significance, without adjustments for multiple comparisons.

RESULTS

Subject Disposition and Demography: Table 2 and Table 3 present subject disposition and demography respectively.

Table 2. Conclusion of Subject Participation Summary (Safety Population)

Conclusion Status Reason[a]	Overall p-Value	MOA-728 12 mg N=179 n(%)	MOA-728 24 mg N=178 n(%)	Placebo N=176 n(%)	Total N=533 n(%)
Total		179 (100)	178 (100)	176 (100)	533 (100)
Completed	0.684	159 (88.83)	160 (89.89)	153 (86.93)	472 (88.56)
Study completed	0.684	159 (88.83)	160 (89.89)	153 (86.93)	472 (88.56)
Discontinued	0.684	20 (11.17)	18 (10.11)	23 (13.07)	61 (11.44)
Adverse event	0.461	7 (3.91)	10 (5.62)	12 (6.82)	29 (5.44)
Lost to follow-up	1.000	2 (1.12)	1 (0.56)	1 (0.57)	4 (0.75)
Other	0.219	0	1 (0.56)	2 (1.14)	3 (0.56)
Protocol violation	0.707	3 (1.68)	1 (0.56)	2 (1.14)	6 (1.13)
Unsatisfactory response - efficacy	0.329	1 (0.56)	0	2 (1.14)	3 (0.56)
Withdrew consent	0.735	7 (3.91)	5 (2.81)	4 (2.27)	16 (3.00)

Overall P-Value: Fisher's Exact Test P-value (2-Tail).
N = total number of subjects; n = number of subjects meeting specified criteria.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

Table 3. Demographic and Baseline Characteristics (Safety Population)

Characteristic	Overall p-Value	Treatment			Total N=533
		MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	
Age (years)					
n		179	178	176	533
Mean	0.883[a]	59.29	59.02	59.69	59.33
Standard deviation		12.53	12.67	13.02	12.72
Minimum		22.00	26.00	28.00	22.00
Maximum		88.00	85.00	91.00	91.00
Sex, n (%)	0.413[b]				
Female		83 (46.37)	86 (48.31)	73 (41.48)	242 (45.40)
Male		96 (53.63)	91 (51.69)	103 (58.52)	291 (54.60)

N = total number of subjects; n = number of subjects meeting criteria.
a. One-way analysis of variance with treatment as factor.
b. P-value for Chi-Square.

Efficacy Results: Table 4 presents time to the first bowel movement in hour by treatment group (primary endpoint). The results show that there were no statistically significant differences in either of the MOA-728 dose groups when compared to placebo.

Table 4. Summary of Time to the First Bowel Movement in Hours by Treatment Group (ITT Population)

Treatment	KM Estimates					Difference (Placebo-MOA)			
	N	Censored, n (%)	Mean (SE)	Median	75th Percentile	Mean	Median	75th Percentile	p-Value[a]
MOA-728 12 mg	180	8 (4.4)	117.1 (4.1)[b]	110.6	140.2	-4.6	-2.1	-6.3	0.502
MOA-728 24 mg	178	3 (1.7)	112 (3.5)	104.6	137.5	-0.4	3.9	-3.7	0.908
Placebo	175	6 (3.4)	112.5 (3.1)[b]	108.5	133.8				

ITT = intent-to-treat; N = total number of subjects; n = number of subjects in specific category; SE = standard error.

a. P-value from log-rank test stratified by region for comparisons of survival distributions for active treatment versus placebo group.

b. Mean and standard error were underestimated.

No further efficacy results are available.

Safety Results: Table 5 and Table 6 present treatment emergent and treatment-related AEs at 5% cutoff respectively.

Table 7 shows SAEs observed during the study. No SAEs were considered related to study treatment.

Table 5. Number and Percentage of Subjects Reporting Treatment-Emergent Adverse Events 5% Cutoff

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			
		MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	Total N=533
Any adverse event	0.326	148 (82.7)	154 (86.5)	142 (80.7)	444 (83.3)
Blood and lymphatic system disorders	0.833	8 (4.5)	8 (4.5)	10 (5.7)	26 (4.9)
Cardiac disorders	0.720	14 (7.8)	17 (9.6)	18 (10.2)	49 (9.2)
Tachycardia	0.519	10 (5.6)	6 (3.4)	10 (5.7)	26 (4.9)
Gastrointestinal disorders	0.183	94 (52.5)	99 (55.6)	81 (46.0)	274 (51.4)
Abdominal pain	0.075	13 (7.3)	12 (6.7)	4 (2.3)	29 (5.4)
Diarrhoea	0.091	3 (1.7)	11 (6.2)	9 (5.1)	23 (4.3)
Nausea	0.042*	62 (34.6)	71 (39.9)	48 (27.3)	181 (34.0)
Retching	0.124	3 (1.7)	9 (5.1)	10 (5.7)	22 (4.1)
Vomiting	0.654	27 (15.1)	21 (11.8)	23 (13.1)	71 (13.3)
General disorders and administration site conditions	0.375	46 (25.7)	53 (29.8)	41 (23.3)	140 (26.3)
Fatigue	0.551	8 (4.5)	12 (6.7)	8 (4.5)	28 (5.3)
Pyrexia	0.919	26 (14.5)	27 (15.2)	24 (13.6)	77 (14.4)
Infections and infestations	0.334	19 (10.6)	12 (6.7)	19 (10.8)	50 (9.4)
Injury, poisoning and procedural complications	0.091	22 (12.3)	14 (7.9)	27 (15.3)	63 (11.8)
Investigations	0.944	40 (22.3)	41 (23.0)	42 (23.9)	123 (23.1)
Metabolism and nutritional disorders	0.471	26 (14.5)	28 (15.7)	20 (11.4)	74 (13.9)
Hypokalemia	0.447	15 (8.4)	11 (6.2)	9 (5.1)	35 (6.6)
Musculoskeletal and connective tissue disorders	0.854	8 (4.5)	10 (5.6)	8 (4.5)	26 (4.9)
Nervous system disorders	0.662	21 (11.7)	26 (14.6)	21 (11.9)	68 (12.8)
Dizziness	0.623	9 (5.0)	10 (5.6)	13 (7.4)	32 (6.0)
Psychiatric disorders	0.929	19 (10.6)	18 (10.1)	20 (11.4)	57 (10.7)
Insomnia	0.418	10 (5.6)	9 (5.1)	5 (2.8)	24 (4.5)
Renal and urinary disorders	0.585	33 (18.4)	35 (19.7)	40 (22.7)	108 (20.3)
Dysuria	0.782	9 (5.0)	12 (6.7)	11 (6.3)	32 (6.0)
Urinary retention	0.578	15 (8.4)	20 (11.2)	20 (11.4)	55 (10.3)
Respiratory, thoracic, and mediastinal disorders	0.254	24 (13.4)	26 (14.6)	16 (9.1)	66 (12.4)
Skin and subcutaneous tissue disorders	0.075	26 (14.5)	14 (7.9)	15 (8.5)	55 (10.3)
Pruritus	0.184	18 (10.1)	9 (5.1)	12 (6.8)	39 (7.3)
Vascular disorders	0.175	11 (6.1)	21 (11.8)	17 (9.7)	49 (9.2)
Hypertension	0.648	8 (4.5)	12 (6.7)	10 (5.7)	30 (5.6)

Non SAEs/SAEs are not separated out.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall p-Value: p-value for Chi-Square.
Statistical significance at the .05 denoted by *.
N = total number of subjects; n = number of subjects with specified event.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

Table 6. Number and Percentage of Subjects Reporting Treatment-Emergent, Treatment-Related Adverse Events , Safety Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment Sequence			
		MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	Total N=533
Any adverse event	0.326	23 (12.8)	30 (16.9)	15 (8.5)	68 (12.8)
Cardiac disorders	0.720	1 (0.6)	4 (2.2)	3 (1.7)	8 (1.5)
Angina pectoris	0.049*	0	2 (1.1)	0	2 (0.4)
Atrial fibrillation	0.170	0	0	1 (0.6)	1 (0.2)
Tachycardia	0.519	1 (0.6)	2 (1.1)	1 (0.6)	4 (0.8)
Ventricular arrhythmia	0.368	0	1 (0.6)	0	1 (0.2)
Ventricular extra systoles	0.359	0	1 (0.6)	1 (0.6)	2 (0.4)
Ventricular tachycardia	0.362	0	0	1 (0.6)	1 (0.2)
Gastrointestinal disorders	0.183	13 (7.3)	12 (6.7)	6 (3.4)	31 (5.8)
Abdominal discomfort	0.369	1 (0.6)	0	0	1 (0.2)
Abdominal distension	0.815	1 (0.6)	1 (0.6)	0	2 (0.4)
Abdominal pain	0.075	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.8)
Abdominal pain lower	0.135	0	2 (1.1)	0	2 (0.4)
Abdominal pain upper	0.007†	0	5 (2.8)	0	5 (0.9)
Constipation	0.159	0	0	1 (0.6)	1 (0.2)
Diarrhoea	0.091	1 (0.6)	3 (1.7)	1 (0.6)	5 (0.9)
Dyspepsia	0.535	1 (0.6)	0	0	1 (0.2)
Flatulence	0.784	1 (0.6)	0	0	1 (0.2)
Frequent bowel movements	0.769	1 (0.6)	0	0	1 (0.2)
Ileus	0.448	0	1 (0.6)	0	1 (0.2)
Nausea	0.054	7 (3.9)	7 (3.9)	4 (2.3)	18 (3.4)
Retching	0.124	0	1 (0.6)	0	1 (0.2)
Vomiting	0.654	3 (1.7)	1 (0.6)	0	4 (0.8)
Vomiting projectile	0.610	1 (0.6)	0	0	1 (0.2)
General disorders and administration site conditions	0.375	1 (0.6)	2 (1.1)	1 (0.6)	4 (0.8)
Feeling abnormal	0.371	1 (0.6)	0	0	1 (0.2)
Pyrexia	0.919	0	2 (1.1)	1 (0.6)	3 (0.6)
Injury, poisoning and procedural complications	0.091	0	0	1 (0.6)	1 (0.2)
Investigations	0.944	2 (1.1)	5 (2.8)	3 (1.7)	10 (1.9)
Alanine aminotransferase increased	0.090	0	2 (1.1)	1 (0.6)	3 (0.6)
Aspartate aminotransferase increased	0.090	0	2 (1.1)	1 (0.6)	3 (0.6)
Blood alkaline phosphatase increased	0.779	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Blood lactate dehydrogenase increased	0.824	1 (0.6)	1 (0.6)	0	2 (0.4)
Blood pressure decreased	0.368	0	1 (0.6)	0	1 (0.2)
Liver function test abnormal	0.368	0	1 (0.6)	0	1 (0.2)
Urine output decreased	0.797	0	0	1 (0.6)	1 (0.2)
Metabolism and nutrition disorders	0.471	1 (0.6)	0	0	1 (0.2)
Hyperkalaemia	0.175	1 (0.6)	0	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0.854	0	1 (0.6)	0	1 (0.2)
Pain in extremity	0.369	0	1 (0.6)	0	1 (0.2)
Nervous system disorders	0.662	1 (0.6)	2 (1.1)	2 (1.1)	5 (0.9)
Dizziness	0.623	0	1 (0.6)	0	1 (0.2)
Headache	0.687	1 (0.6)	1 (0.6)	2 (1.1)	4 (0.8)
Psychiatric disorders	0.929	1 (0.6)	2 (1.1)	1 (0.6)	4 (0.8)
Delirium	0.360	0	0	1 (0.6)	1 (0.2)
Insomnia	0.418	1 (0.6)	1 (0.6)	0	2 (0.4)
Mental status changes	0.368	0	1 (0.6)	0	1 (0.2)
Renal and urinary disorders	0.585	4 (2.2)	1 (0.6)	1 (0.6)	6 (1.1)
Dysuria	0.782	1 (0.6)	0	0	1 (0.2)
Pollakiuria	0.604	1 (0.6)	0	0	1 (0.2)
Urinary retention	0.578	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.8)

Table 6. Number and Percentage of Subjects Reporting Treatment-Emergent, Treatment-Related Adverse Events , Safety Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment Sequence			
		MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	Total N=533
Respiratory, thoracic and mediastinal disorders	0.254	2 (1.1)	0	0	2 (0.4)
Hiccups	0.613	2 (1.1)	0	0	2 (0.4)
Skin and subcutaneous tissue disorders	0.075	3 (1.7)	4 (2.2)	1 (0.6)	8 (1.5)
Hyperhidrosis	0.454	0	1 (0.6)	0	1 (0.2)
Pruritus	0.184	2 (1.1)	3 (1.7)	1 (0.6)	6 (1.1)
Pruritus generalized	0.372	1 (0.6)	0	0	1 (0.2)
Rash	0.769	0	1 (0.6)	0	1 (0.2)
Vascular disorders	0.175	1 (0.6)	4 (2.2)	0	5 (0.9)
Hypertension	0.648	1 (0.6)	0	2 (1.1)	3 (0.6)
Hypotension	0.905	0	2 (1.1)	0	2 (0.4)
Labile hypertension	0.135	0	2 (1.1)	0	2 (0.4)

Non SAEs/SAEs are not separated out.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall p-Value: p-value for Chi-Square.
N = total number of subjects; n = number of subjects with specified event.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

Table 7. Number (%) of Subjects Reporting Serious Adverse Events, Safety Population

System Organ Class[a] Preferred Term	Treatment Sequence				
	Overall p-Value	MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	Total N=533
Any adverse event	0.775	22 (12.3)	23 (12.9)	26 (14.8)	71 (13.3)
Blood and lymphatic system disorders	0.371	1 (0.6)	0	0	1 (0.2)
Anaemia	0.371	1 (0.6)	0	0	1 (0.2)
Cardiac disorders	0.867	2 (1.1)	3 (1.7)	2 (1.1)	7 (1.3)
Acute myocardial infarction	0.602	0	1 (0.6)	1 (0.6)	2 (0.4)
Atrial fibrillation	0.362	0	0	1 (0.6)	1 (0.2)
Cardiac arrest	0.371	1 (0.6)	0	0	1 (0.2)
Cardiopulmonary failure	0.368	0	1 (0.6)	0	1 (0.2)
Cardiovascular disorder	0.371	1 (0.6)	0	0	1 (0.2)
Tachyarrhythmia	0.368	0	1 (0.6)	0	1 (0.2)
Endocrine disorders	0.371	1 (0.6)	0	0	1 (0.2)
Steroid withdrawal syndrome	0.371	1 (0.6)	0	0	1 (0.2)
Gastrointestinal disorders	0.532	5 (2.8)	7 (3.9)	9 (5.1)	21 (3.9)
Abdominal adhesions	0.371	1 (0.6)	0	0	1 (0.2)
Abdominal pain	0.371	1 (0.6)	0	0	1 (0.2)
Colonic fistula	0.362	0	0	1 (0.6)	1 (0.2)
Constipation	0.131	0	0	2 (1.1)	2 (0.4)
Diarrhoea	0.362	0	0	1 (0.6)	1 (0.2)
Gastrointestinal fistula	0.368	0	1 (0.6)	0	1 (0.2)
Haemorrhoids	0.362	0	0	1 (0.6)	1 (0.2)
Ileus	1.000	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Ileus paralytic	0.368	0	1 (0.6)	0	1 (0.2)
Intestinal obstruction	0.368	0	1 (0.6)	0	1 (0.2)
Intestinal strangulation	0.362	0	0	1 (0.6)	1 (0.2)
Mechanical ileus	0.368	0	1 (0.6)	0	1 (0.2)
Rectal haemorrhage	0.368	0	1 (0.6)	0	1 (0.2)
Small intestinal obstruction	0.784	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.8)
Vomiting	0.362	0	0	1 (0.6)	1 (0.2)
General disorders and administration site condition site	0.372	2 (1.1)	1 (0.6)	0	3 (0.6)
Chest pain	0.371	1 (0.6)	0	0	1 (0.2)
Multi organ failure	0.371	1 (0.6)	0	0	1 (0.2)
Pyrexia	0.368	0	1 (0.6)	0	1 (0.2)
Hepatobiliary disorders	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Cholecystitis acute	0.362	0	0	1 (0.6)	1 (0.2)
Cholestasis	0.371	1 (0.6)	0	0	1 (0.2)
Infections and infestations	0.436	3 (1.7)	7 (3.9)	5 (2.8)	15 (2.8)
Abdominal abscess	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Abdominal infection	0.371	1 (0.6)	0	0	1 (0.2)
Pelvic abscess	0.368	0	1 (0.6)	0	1 (0.2)
Pneumonia	0.812	1 (0.6)	2 (1.1)	2 (1.1)	5 (0.9)
Postoperative wound infection	0.369	1 (0.6)	2 (1.1)	0	3 (0.6)
Septic shock	0.362	0	0	1 (0.6)	1 (0.2)
Subdiaphragmatic abscess	0.362	0	0	1 (0.6)	1 (0.2)
Urinary tract infection	0.368	0	1 (0.6)	0	1 (0.2)
Wound infection	0.368	0	1 (0.6)	0	1 (0.2)
Injury, poisoning and procedural complications	0.816	7 (3.9)	7 (3.9)	9 (5.1)	23 (4.3)
Abdominal wound dehiscence	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Anastomotic leak	0.894	3 (1.7)	3 (1.7)	4 (2.3)	10 (1.9)
Post procedural haemorrhage	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Postoperative ileus	0.372	2 (1.1)	1 (0.6)	0	3 (0.6)
Wound dehiscence	0.216	0	3 (1.7)	3 (1.7)	6 (1.1)

Table 7. Number (%) of Subjects Reporting Serious Adverse Events, Safety Population

System Organ Class[a] Preferred Term	Treatment Sequence				
	Overall p-Value	MOA-728 12 mg N=179	MOA-728 24 mg N=178	Placebo N=176	Total N=533
Wound evisceration	0.362	0	0	1 (0.6)	1 (0.2)
Wound secretion	0.371	1 (0.6)	0	0	1 (0.2)
Investigations	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Oxygen saturation decreased	0.604	1 (0.6)	0	1 (0.6)	2 (0.4)
Metabolism and nutrition disorders	0.360	1 (0.6)	0	2 (1.1)	3 (0.6)
Dehydration	0.362	0	0	1 (0.6)	1 (0.2)
Hyperkalaemia	0.362	0	0	1 (0.6)	1 (0.2)
Hypoglycaemia	0.371	1 (0.6)	0	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0.368	0	1 (0.6)	0	1 (0.2)
Fistula	0.368	0	1 (0.6)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.879	3 (1.7)	2 (1.1)	3 (1.7)	8 (1.5)
Colon cancer	0.879	3 (1.7)	2 (1.1)	3 (1.7)	8 (1.5)
Renal and urinary disorders	0.137	2 (1.1)	0	0	2 (0.4)
Renal failure acute	0.371	1 (0.6)	0	0	1 (0.2)
Renal impairment	0.371	1 (0.6)	0	0	1 (0.2)
Reproductive system and breast disorders	0.362	0	0	1 (0.6)	1 (0.2)
Pelvic fluid collection	0.362	0	0	1 (0.6)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0.128	0	2 (1.1)	4 (2.3)	6 (1.1)
Atelectasis	0.362	0	0	1 (0.6)	1 (0.2)
Pulmonary embolism	0.602	0	1 (0.6)	1 (0.6)	2 (0.4)
Respiratory depression	0.362	0	0	1 (0.6)	1 (0.2)
Respiratory failure	0.602	0	1 (0.6)	1 (0.6)	2 (0.4)
Vascular disorders	0.368	0	1 (0.6)	0	1 (0.2)
Hemorrhage	0.368	0	1 (0.6)	0	1 (0.2)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall p-Value: p-value for Chi-Square.
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 or more different adverse events within the higher level category.

Three (3) subjects died due to AEs, all of which were considered unrelated to study treatment. One (1) subject in the placebo group died from respiratory failure, 1 subject in the MOA-728 12 mg group died from multi-organ failure, pneumonia and renal impairment and 1 subject in the MOA-728 24 mg group died from respiratory failure and cardiopulmonary failure.

Thirty-two (32) subjects discontinued due to AEs. Seven (7) subjects discontinued due to AEs which were considered related to study treatment.

Twenty-six (26/178) , 30/178, and 33/176 subjects were observed with laboratory results of potentially clinical importance in the MOA-728, 12 mg, MOA-728 24 mg and placebo groups respectively.

One hundred and forty-three (143/179), 151/178, and 136/176 subjects were observed to have clinically important vital signs in the MOA-728, 12 mg, MOA-728 24 mg and placebo group respectively.

One hundred (100/170) , 116/171, and 103/173 subjects were observed to have clinically important ECG results in MOA-728, 12 mg, MOA-728 24 mg and placebo group respectively.

Of the 532 subjects in the safety population who had laboratory evaluations performed, a total of 89 (16.7%) had PCI laboratory test values, with no significant differences observed among the treatment groups. The most common PCI laboratory test results were: low lymphocyte count (27 subjects, 5.1% [7, 4.0%] in the 12-mg; [9, 5.1%] in the 24-mg treatment group; and [11, 6.3%] in the placebo group), low levels of potassium (18 subjects, 3.4% [6, 3.4%] in the 12-mg; [8, 4.5%] in the 24-mg treatment group; and [4, 2.3%] in the placebo group).

Vital sign measurements (body temperature, pulse rate, blood pressure [BP], and respiration) were recorded at screening, day of surgery, immediately prior to test article administration and at the end of test article administration for the first dose of test article on Days 1, 2, and 3, once daily during double-blind treatment after Day 3, and End of Treatment. A total of 430 (80.7%) subjects had PCI changes in vital sign measurements. Overall, a review of vital signs revealed a higher incidence of PCI decreases in supine systolic BP (>20%) and a mean decrease in BP (postrelative to preinfusion) for the 24-mg dose group. In the MOA-728 24-mg treatment group significant decreases from baseline in adjusted mean value for supine systolic BP in the range of -6.42 to -18.31 mm Hg ($p<0.001$) were observed. The number of subjects with PCI decreases in supine systolic BP measurements was significantly different (p-value=0.007; 102 subjects [27, 15.4%] in the 12-mg, [48, 27.4%] in the 24-mg treatment group, and [27, 15.6%] in the placebo group) among treatment groups.

On Day 1 (the first dose of test article), an ECG was performed prior to and following the completion of the initial test article infusion. On Day 2 and 3, an ECG was performed prior to and after the first or second test article infusion (depending on time of infusions). A 12-lead ECG was required for all time points. Of the 514 subjects in the safety population who had ECGs performed, a total of 319 (62.1%) subjects had PCI ECG findings, with no significant differences observed among the treatment groups. There were no safety signals identified.

CONCLUSIONS: This study was designed to assess MOA-728 for the treatment of POI when administered IV. This study failed due to lack of efficacy. The results for the primary efficacy endpoint showed that there were no statistically significant differences observed in either MOA-728 dose group when compared with placebo.

Analyses of safety showed that MOA-728 was safe and well tolerated at 12 mg and 24 mg (IV) doses.