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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Relistor® / Methylnaltrexone

PROTOCOL NO.: 3200L2-301-WW (B2541008)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Intravenous Methylnaltrexone (MOA-728) for the Treatment of Postoperative Ileus After Ventral Hernia Repair

Study Centers: In total 98 centers in 11 countries took part in the study and randomized subjects including 2 sites in Australia, 2 in Belgium, 3 in Canada, 4 in Germany, 4 in Hungary, 4 in Italy, 1 in the Republic of Korea, 2 in the Netherlands, 3 in Poland, 7 in South Africa, and 66 in the United States (US).

Study Initiation and Final Completion Dates: 27 August 2007 to 02 December 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To assess the efficacy of intravenous (IV) MOA-728 in subjects who had undergone repair of large (≥10 cm) ventral hernias, with or without a mesh prosthesis via laparotomy or laparoscopy.

Secondary Objectives: 1) To assess the safety of IV MOA-728 administered approximately every 6 hours in these post-surgical subjects and 2) to examine clinically meaningful events for nausea or retching/vomiting at 24 hours after the first dose as evaluated 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 2 different dose regimens (12 mg and 24 mg) of IV MOA-728 compared with those of placebo in shortening the time to return of bowel function in subjects receiving opioid analgesia administered via patient-controlled analgesia (PCA), who had undergone repair of large (≥10 cm) ventral hernias with or without a mesh prosthesis via laparotomy or laparoscopy. Subjects participated in the study for approximately 7 weeks (Table 1).

Subjects signed and dated an informed consent form and were screened at a preoperative visit up to 21 days before surgery. Those who met all screening inclusion/exclusion criteria

continued in the study. Subjects underwent general anesthesia. Epidural and spinal anesthesia/analgesia were not permitted.

After surgery, subjects who met postoperative requirements for continuation were randomly assigned to 1 of 3 treatments: MOA-728 24 mg, MOA-728 12 mg, or placebo. At the time of randomization, subjects were prospectively stratified by region and type of surgery (laparotomy or laparoscopy). Subjects received their first dose of test article (per the postoperative randomization assignment) within approximately 90 minutes after the end of surgery (defined as the time when the last skin suture or staple was placed in the subject). Postoperative pain was managed via PCA with IV morphine, hydromorphone, or fentanyl. Subjects received test article approximately every 6 hours (q6h) until 1 of the following occurred: 1) 24 hours passed after the subject was tolerating clear liquids and had the first bowel movement; 2) the subject was discharged or withdrawn; or 3) a maximum of 10 days had elapsed. A series of health outcomes assessments were also performed. A follow-up office visit occurred approximately 7 days after the last dose of test article and a follow-up telephone contact occurred approximately 15 days after the last dose of test article.

Table 1. Study Flowchart

Study Day	**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**					**End of Treatment[a]**	**Follow-Up**	
		PreOp	**PostOp**			**Double-Blind Treatment Period**			
Assessment	**Screening**	**Day of Surgery**	**After Surgery**	**Before Test Article**	**After Test Article**	**Assessments While on Test Article**		**Follow-Up[b] Day 7**	**Follow-up[b] Day 15**
Informed consent	X								
Inclusion/exclusion and postop continuation 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	X	
Laboratory tests[d]	X					X	X	X	
Pregnancy test[e]	X[e]	X[e]							
ECG[f]	X			X	X	X[f]	X		
Randomization			X						
IV PCA administration[g]			X		X	X			
Clinical assessments[h]					X	X			
Test article IV administration[i]					X	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	X
Patient abdominal pain VAS[l]				X	X	X	X		
EQ-5D General Health Scale[m]	X					X[m]	X		
Opioid-Related Symptom Distress Scale (SDS)[n]						X[n]	X		

Table 1. Study Flowchart

Study Day	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					End of Treatment[a]	Follow-Up	
		PreOp	PostOp			Double-Blind Treatment Period			
Assessment	Screening	Day of Surgery	After Surgery	Before Test Article	After Test Article	Assessments While on Test Article		Follow-Up[b] Day 7	Follow-up[b] Day 15

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; Preop = preoperative; Postop = postoperative; SDS = Symptom Distress Scale; VAS = visual analog scale.

a. The end-of-treatment assessment was conducted 24 hours after the subject had the first bowel movement and was able tolerate at least clear liquids, or when a subject was discharged from the hospital, or after 10 days of treatment had elapsed, or when the subject had been withdrawn 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 after the last dose of test article.
c. Vital signs (body temperature, pulse rate, BP, respiratory rate) were taken immediately before and at the end of the first dose of test article administration on Day 1, before and after any 1 dose on Days 2, and 3, and once daily thereafter. Subjects were to be resting before vital signs were taken. Height and weight were taken at screening.
d. If >1 laboratory panel was performed during the day of assessment, the last full panel that was performed was to be recorded. If the subject was still in the hospital, specimens for LFT analysis only collected on study Days 2, 5, and 8; no other labs were required on Days 2, 5, and 8. Labs were not required on Days 3, 4, 6, 7, 9, or 10 except the End of Treatment labs when appropriate.
e. A serum pregnancy test was required at the time of screening. A urine or serum pregnancy test was required within 72 hours before dose administration.
f. A 12-lead ECG was required at screening and at the end of treatment. On Day 1 (the first dose of test article), a 12-lead ECG was performed before and after the initial test article infusion. On Day 2 or 3 a 12-lead ECG was performed before and after any 1 dose of test article administration.
g. Subjects had access to IV opioid PCA for the duration of the study starting after surgery and continuing until 24 hours after the subject had his or her first bowel movement and was tolerating clear liquids, for a maximum of 10 days during which the subject was not tolerating at least clear liquids and was not having a bowel movement, or until the subject was discharged or withdrew early from the study for 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 tube, OG tube or indwelling urinary catheter. The time of discharge (time when the discharge order was written) was recorded as part of these assessments.
i. Subjects received their first dose of test article within approximately 90 minutes after the end of the surgery. Test article treatment was administered approximately every 6 hours until 24 hours after the subject had had his or her first bowel movement and was tolerating clear liquids, for a maximum of 10 days during which the subject was not tolerating at least clear liquids and was not having a bowel movement, or until the subject was discharged or withdrew early from the study for any reason.
j. Surgical treatment assessment data collected included all intraoperative medication, and blood components; all opioid medications; the duration of the procedure and time of the end of procedure (when the last skin suture or staple was placed in the subject); and the volume of blood lost.
k. Adverse events were collected from the signing of the informed consent form through the Day 15 follow-up visit.
l. The abdominal pain VAS was completed by the subject before the initial dose of test article (if the subject was awake and alert); after each dose of test article on Day 1; and then daily after the first or second dose (depending on timing of doses) of test article on each day thereafter.
m. EQ-5D General Health Scale was completed by the subject at screening, on Day 2 of test article administration, 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): It was planned to randomize 360 subjects (120 per treatment group) in this study. Of these, 374 subjects were randomized and 373 subjects received test article (124 received MOA-728 12 mg, 125 received MOA-728 24 mg, and 124 received placebo) and were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Males and females, aged ≥18 years;
- Scheduled for ventral wall hernia repair with general anesthesia;
- Met the American Society of Anesthesiologists physical status I, II, or III.

Exclusion Criteria:

- Received investigational drug or procedure within 30 days of randomization;
- Women who were pregnant or lactating;
- Calculated creatinine clearance (Cockcroft-Gault GRF) ≤50 mL/min.

Study Treatment: Sterile MOA-728 or placebo for injection was supplied in doses of 12 mg or 24 mg as lyophilized white powder in needle-less spikeable vials along with 50 mL bags of normal saline for reconstitution. Subjects were randomly assigned to receive either MOA-728 (12 mg or 24 mg) or placebo. The test article was infused over a period of approximately 20 minutes. The first dose of test article was to be administered within approximately 90 minutes after completion of the surgical procedure as defined as the time when the last skin suture or staple is placed in the subject. Doses were administered approximately q6h for a total of 4 doses in a 24-hour period. Dose administration with MOA-728 could continue 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 was placed in the subject).

Key Secondary Endpoints:

- Time to discharge eligibility (defined as tolerance of oral intake of liquids >500 mL per 8 hours from the end of surgery);
- 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 SDS.

Safety Evaluations: Safety assessments involved the monitoring and recording of all adverse events (AEs) and serious AEs (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 population was the primary population for efficacy analysis.

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

Primary Endpoint:

The primary efficacy endpoint was the time to the first bowel movement from the end of the surgical procedure (defined as the time when the last suture or staple was placed in the subject). 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 type of surgery (laparotomy and laparoscopy) and geographical region. Two (2) comparisons were made: MOA-728 24 mg versus (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. Additional exploratory analyses were performed to examine the primary efficacy endpoint response with respect to clinically relevant demographic and baseline variables (type of surgical procedure and region).

Secondary Endpoints:

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

The multiplicity among the primary endpoint and key secondary efficacy endpoints was also controlled using a closed sequential procedure.

Absolute SDS values at various time points were compared between the IV MOA-728 and placebo groups. The overall composite SDS score was the mean of each of the 10 individual symptom SDS scores. By taking the mean score of all 10 symptoms in each dimension, dimension-specific composite SDS scores for frequency, severity, and bothersomeness were created.

RESULTS

Subject Disposition and Demography: A total of 374 subjects were randomized in the study. One (1) subject was randomized but not treated. There were 124 subjects in the IV MOA-728 12 mg treatment group, 125 subjects in the IV MOA-728 24 mg treatment group, and 124 subjects in the placebo group. A total of 325 subjects completed the study: 110 (88.71%) subjects in the IV MOA-728 12 mg treatment group, 110 subjects (88.00%) in the IV MOA-728 24 mg treatment group, and 105 (84.68%) subjects in the placebo group. Table 2 presents subject disposition.

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

Conclusion Status Reason[a]	Treatment				Total N=373
	Overall p-Value	MOA-728 12 mg n=124	MOA-728 24 mg n=125	Placebo n=124	
Total		124 (100)	125 (100)	124 (100)	373 (100)
Completed	0.639	110 (88.71)	110 (88.00)	105 (84.68)	325 (87.13)
Study completed	0.639	110 (88.71)	110 (88.00)	105 (84.68)	325 (87.13)
Discontinued	0.639	14 (11.29)	15 (12.00)	19 (15.32)	48 (12.87)
Adverse event	0.766	6 (4.84)	8 (6.40)	5 (4.03)	19 (5.09)
Lost to follow-up	0.665	0	0	1 (0.81)	1 (0.27)
Other	1.000	2 (1.61)	3 (2.40)	3 (2.42)	8 (2.14)
Protocol violation	0.321	2 (1.61)	1 (0.80)	4 (3.23)	7 (1.88)
Unsatisfactory response-efficacy	0.665	0	0	1 (0.81)	1 (0.27)
Withdrawal consent	0.718	4 (3.23)	3 (2.40)	5 (4.03)	12 (3.22)

Overall P-Value: Fisher's Exact Test P-value (2-Tail).
MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in treatment group.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

A slight majority of subjects were women (52.82%), and most were White (89.81%). The mean age of the subjects was 56.05 years. Most of the subjects had an open laparotomy (82.84%). Table 3 presents subject demography.

Table 3. Demographic and Baseline Characteristics (Safety Population)

Characteristic		Treatment			
	Overall p-Value	MOA-728 12 mg n=124	MOA-728 24 mg n=125	Placebo n=124	Total N=373
Age (years)					
N		124	125	124	373
Mean	0.514[a]	57.11	55.21	55.82	56.05
Standard deviation		13.25	13.05	13.52	13.26
Minimum		18.00	21.00	25.00	18.00
Maximum		84.00	83.00	85.00	85.00
Sex, N (%)	0.817[b]				
Female		63 (50.81)	66 (52.80)	68 (54.84)	197 (52.82)
Male		61 (49.19)	59 (47.20)	56 (45.16)	176 (47.18)

MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in treatment group.
a. One-way analysis of variance with treatment as factor.
b. P-value for Chi-Square.

Efficacy Results: Table 4 presents a summary of time to the first bowel movement by treatment group.

Table 5, Table 6 and Table 7 present the results for the secondary endpoints.

The results showed that there were no statistically significant differences in either of the IV MOA-728 treatment groups when compared with placebo for any of these endpoints.

Table 4. Summary of Time to the First Bowel Movement by Treatment Group - mITT Population

Surgery Type	Region	Treatment	N	Censored n (%)	KM Estimates			Difference (MOA-Placebo)			
					Mean (SE)	Median	75th Percentile	Mean	Median	75th Percentile	p-Value[a]
All surgery	All regions	MOA-728 12 mg	124	5 (4.0)	93.3 (3.2)	88.4	114.9	2.0	3.7	8.0	0.944
		MOA-728 24 mg	125	5 (4.0)	100.4 (4.2)	93.7	117.8	9.1	9.0	10.8	0.208
		Placebo	124	4 (3.2)	91.3 (3.9)	84.7	106.9				
Laparoscopic	EU/SA/AP	MOA-728 12 mg	2	0	100.8 (41.3)	100.8	142.1	47.6	46.7	70.3	
		MOA-728 24 mg	3	0	141.4 (62.1)	116.1	259.3	88.3	62.0	187.4	
		Placebo	3	0	53.1 (11.1)	54.1	71.8				
	Northern America	MOA-728 12 mg	18	0	94.9 (10.8)	91.5	118.6	11.5	11.4	22.1	
		MOA-728 24 mg	20	2 (10.0)	106.5 (9.2)	104.5	118.9	23.2	24.5	22.4	
		Placebo	18	0	83.4 (7.5)	80.0	96.5				
Open	EU/SA/AP	MOA-728 12 mg	53	1 (1.9)	83.3 (3.8)	76.3	95.8	-3.3	0.3	-9.3	
		MOA-728 24 mg	54	1 (1.9)	88.6 (6.0)	82.1	100.2	2.1	6.1	-4.8	
		Placebo	55	0	86.6 (4.6)	75.9	105.0				
	Northern America	MOA-728 12 mg	51	4 (7.8)	103.0 (5.1)	92.7	120.7	0.0	2.9	4.8	
		MOA-728 24 mg	48	2 (4.2)	108.2 (6.2)	99.1	134.2	5.2	9.3	18.2	
		Placebo	48	4 (8.3)	103.0 (8.3)	89.8	116.0				

EU/SA/AP = Europe, South Africa and Asia-Pacific; KM = Kaplan-Meier; mITT = modified intent-to-treat; MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in specific category; SE = standard error; vs = versus.

a. P-value from log-rank test stratified by surgery type and region for comparisons of survival distributions for active MOA vs placebo group.

Table 5. Summary of Time to Discharge Eligibility by Treatment Group - mITT Population

Surgery Type	Region	Treatment	N	Censored n (%)	KM Estimates			Difference (MOA-Placebo)			
					Mean (SE)	Median	75th Percentile	Mean	Median	75th Percentile	p-Value[a]
All surgery	All regions	MOA-728 12 mg	124	5 (4.0)	44.9 (2.9)	41.7	59.9	3.6	14.7	7.1	0.553
		MOA-728 24 mg	125	1 (0.8)	51.4 (5.1)	36.4	65.3	10.0	9.4	12.5	0.058
		Placebo	124	0	41.4 (3.4)	27.0	52.8				
Laparoscopic	EU/SA/AP	MOA-728 12 mg	2	0	34.5 (11.9)	34.5	46.4	-7.4	-14.9	-4.7	
		MOA-728 24 mg	3	0	55.2 (13.1)	66.3	70.3	13.4	16.8	19.2	
		Placebo	3	0	41.9 (8.4)	49.4	51.1				
	Northern America	MOA-728 12 mg	18	0	30.6 (5.6)	24.4	43.8	9.4	11.6	20.5	
		MOA-728 24 mg	20	0	37.3 (5.7)	29.8	48.9	16.2	17.0	25.6	
		Placebo	18	0	21.1 (5.4)	12.8	23.3				
Open	EU/SA/AP	MOA-728 12 mg	53	1 (1.9)	39.2 (3.1)	31.4	51.4	-2.1	0.9	-14.6	
		MOA-728 24 mg	54	1 (1.9)	44.4 (3.9)[b]	31.6	50.8	3.1	1.1	-15.2	
		Placebo	55	0	41.3 (3.0)	30.5	66.0				
	Northern America	MOA-728 12 mg	51	4 (7.8)	56.9 (5.8)	48.5	77.6	7.9	22.2	12.2	
		MOA-728 24 mg	48	0	58.7 (9.2)	45.5	70.3	9.7	19.3	4.9	
		Placebo	48	0	49.0 (7.7)	26.2	65.4				

EU/SA/AP = Europe, South Africa and Asia-Pacific; KM = Kaplan-Meier; mITT = modified intent-to-treat; MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in specific category; SE = standard error; vs = versus.

a. P-value from log-rank test stratified by surgery type and region for comparisons of survival distributions for active MOA vs placebo group.

b. Mean and SE were underestimated.

Table 6. Summary of Time to the Discharge Order Written by Treatment Group - mITT Population

Surgery Type	Region	Treatment	N	Censored n (%)	KM Estimates			Difference (MOA-Placebo)			
					Mean (SE)	Median	75th Percentile	Mean	Median	75th Percentile	p-Value[a]
All surgery	All regions	MOA-728 12 mg	124	5 (4.0)	130.6 (15.5)	97.7	136.0	-2.3	1.1	-7.8	0.806
		MOA-728 24 mg	125	2 (1.6)	123.8 (6.8)	113.3	141.5	-9.1	16.7	-2.3	0.355
		Placebo	124	2 (1.6)	132.9 (14.1)	96.6	143.8				
Laparoscopic	EU/SA/AP	MOA-728 12 mg	2	0	127.0 (38.6)	127.0	165.6	35.3	61.2	19.8	
		MOA-728 24 mg	3	0	118.3 (29.2)	114.3	170.8	26.6	48.4	25.0	
		Placebo	3	0	91.7 (27.1)	65.8	145.8				
	Northern America	MOA-728 12 mg	18	0	73.7 (9.0)	68.6	93.7	8.1	0.2	22.8	
		MOA-728 24 mg	20	0	88.1 (8.6)	83.1	118.8	22.4	14.7	47.9	
		Placebo	18	0	65.6 (5.6)	68.4	70.9				
Open	EU/SA/AP	MOA-728 12 mg	53	1 (1.9)	158.1 (32.7)	116.0	142.5	26.5	-5.0	-22.3	
		MOA-728 24 mg	54	1 (1.9)	131.4 (10.8)	113.8	145.3	-0.3	-7.2	-19.5	
		Placebo	55	1 (1.8)	131.6 (8.2)[b]	121.0	164.8				
	Northern America	MOA-728 12 mg	51	4 (7.8)	121.2 (11.8)	101.2	136.0	-26.9	6.7	-7.6	
		MOA-728 24 mg	48	1 (2.1)	129.9 (11.4)	116.6	148.0	-18.2	22.1	4.4	
		Placebo	48	1 (2.1)	148.1 (29.3)	94.5	143.6				

EU/SA/AP = Europe, South Africa and Asia-Pacific; KM = Kaplan-Meier; mITT = modified intent-to-treat; MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in specific category; SE = standard error; vs = versus.

a. P-value from log-rank test stratified by surgery type and region for comparisons of survival distributions for active MOA vs placebo group.

b. Mean and SE were underestimated.

Table 7. Summary of SDS CME for Nausea or Retching/Vomiting at Day 2 (24 Hours) - mITT Population, (Observed-Case Analysis)

Surgery Type	Region	Treatment	N	n (%)	p-Value[a]
All surgery	All regions	MOA-728 12 mg	115	10 (8.7)	0.460
		MOA-728 24 mg	113	19 (16.8)	0.013
		Placebo	113	7 (6.2)	
Laparoscopic	EU/SA/AP	MOA-728 12 mg	2	1 (50.0)	
		MOA-728 24 mg	3	0 (0.0)	
		Placebo	3	0 (0.0)	
	Northern America	MOA-728 12 mg	16	1 (6.3)	
		MOA-728 24 mg	16	4 (25.0)	
		Placebo	15	2 (13.3)	
Open	EU/SA/AP	MOA-728 12 mg	53	4 (7.5)	
		MOA-728 24 mg	53	10 (18.9)	
		Placebo	54	3 (5.6)	
	Northern America	MOA-728 12 mg	44	4 (9.1)	
		MOA-728 24 mg	41	5 (12.2)	
		Placebo	41	2 (4.9)	

CME = clinically meaningful events; CMH = Cochran-Mantel-Haenszel; EU/SA/AP = Europe, South Africa and Asia-Pacific; mITT = modified intent-to-treat; MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in specific category; SDS = Symptom Distress Scale; vs = versus.

a. P-value based on CMH Chi-Square test stratified by surgery type and region for MOA group vs Placebo group.

Safety Results:

Adverse Events: A total of 286 (76.7%) subjects reported ≥1 treatment-emergent AEs (TEAEs): 90 (72.6%) in the IV MOA-728 12 mg treatment group, 97 (77.6%) in the IV MOA-728 24 mg treatment group, and 99 (79.8%) in the placebo group. Table 8 presents TEAEs.

A total of 67 subjects (18.0%) reported TEAEs that were considered by the Investigator as related to the test article, including 25 (20.2%) in the IV MOA-728 12 mg treatment group, 27 (21.6%) in the IV MOA-728 24 mg treatment group, and 15 (12.1%) in the placebo group.

Serious Adverse Events: Table 9 presents SAEs observed during the study. Data not available for treatment-related SAEs.

Table 8. Number (%) of Subjects Reporting Treatment Emergent Adverse Events 5% Cut-off - Safety Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total N=373
		MOA-728 12 mg n=124	MOA-728 24 mg n=125	Placebo n=124	
Any adverse event	0.384	90 (72.6)	97 (77.6)	99 (79.8)	286 (76.7)
Cardiac disorders	0.311	6 (4.8)	8 (6.4)	12 (9.7)	26 (7.0)
Tachycardia	0.129	4 (3.2)	3 (2.4)	9 (7.3)	16 (4.3)
Gastrointestinal disorders	0.742	57 (46.0)	55 (44.0)	51 (41.1)	163 (43.7)
Constipation	0.809	10 (8.1)	13 (10.4)	11 (8.9)	34 (9.1)
Nausea	0.824	39 (31.5)	35 (28.0)	38 (30.6)	112 (30.0)
Vomiting	0.609	16 (12.9)	21 (16.8)	21 (16.9)	58 (15.5)
General disorders and administration site conditions	0.690	28 (22.6)	23 (18.4)	27 (21.8)	78 (20.9)
Fatigue	0.071	7 (5.6)	1 (0.8)	3 (2.4)	11 (2.9)
Pyrexia	0.800	18 (14.5)	15 (12.0)	18 (14.5)	51 (13.7)
Infections and infestations	0.446	9 (7.3)	6 (4.8)	11 (8.9)	26 (7.0)
Injury, poisoning and procedural complications	0.425	8 (6.5)	7 (5.6)	12 (9.7)	27 (7.2)
Investigations	0.642	20 (16.1)	15 (12.0)	18 (14.5)	53 (14.2)
Metabolism and nutrition disorders	0.269	10 (8.1)	16 (12.8)	9 (7.3)	35 (9.4)
Hypokalaemia	0.127	4 (3.2)	10 (8.0)	4 (3.2)	18 (4.8)
Nervous system disorders	0.359	17 (3.7)	17 (13.6)	24 (19.4)	58 (15.5)
Dizziness	0.626	7 (5.6)	4 (3.2)	5 (4.0)	16 (4.3)
Headache	0.462	8 (6.5)	9 (7.2)	13 (10.5)	30 (8.0)
Somnolence	0.098	7 (5.6)	1 (0.8)	6 (4.8)	14 (3.8)
Psychiatric disorders	0.331	14 (11.3)	9 (7.2)	8 (6.5)	31 (8.3)
Renal and urinary disorders	0.556	15 (12.1)	18 (14.4)	21 (16.9)	54 (14.5)
Urinary retention	0.897	12 (9.7)	10 (8.0)	11 (8.9)	33 (8.8)
Respiratory, thoracic and mediastinal disorders	0.655	12 (9.7)	16 (12.8)	12 (9.7)	40 (10.7)
Dyspnoea	0.287	3 (2.4)	7 (5.6)	3 (2.4)	13 (3.5)
Skin and subcutaneous tissue disorders	0.108	19 (15.3)	11 (8.8)	22 (17.7)	52 (13.9)
Pruritus	0.389	17 (13.7)	11 (8.8)	17 (13.7)	45 (12.1)
Vascular disorders	0.704	12 (9.7)	14 (11.2)	10 (8.1)	36 (9.7)
Hypertension	0.493	4 (3.2)	8 (6.4)	7 (5.6)	19 (5.1)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall P-value: Refers to No. of Subjects data. P-value for Chi-Square.
MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in each treatment group; No = number.
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 ≥2 different adverse events within the higher level category.

Table 9. Number (%) of Subjects Reporting Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total N=373
		MOA-728 12 mg n=124	MOA-728 24 mg n=125	Placebo n=124	
Any adverse event	0.157	20 (16.1)	17 (13.6)	28 (22.6)	65 (17.4)
Blood and lymphatic system disorders	0.133	0	0	2 (1.6)	2 (0.5)
Anaemia	0.133	0	0	2 (1.6)	2 (0.5)
Coagulopathy	0.365	0	0	1 (0.8)	1 (0.3)
Cardiac disorders	0.364	0	1 (0.8)	2 (1.6)	3 (0.8)
Supraventricular tachycardia	0.365	0	0	1 (0.8)	1 (0.3)
Tachycardia	0.606	0	1 (0.8)	1 (0.8)	2 (0.5)
Gastrointestinal disorders	0.308	2 (1.6)	6 (4.8)	6 (4.8)	14 (3.8)
Abdominal hernia	0.365	0	0	1 (0.8)	1 (0.3)
Abdominal pain	1.000	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.8)
Abdominal pain upper	0.370	0	1 (0.8)	0	1 (0.3)
Abdominal wall haematoma	0.370	0	1 (0.8)	0	1 (0.3)
Diarrhoea	0.365	0	0	1 (0.8)	1 (0.3)
Enterocutaneous fistula	0.365	0	0	1 (0.8)	1 (0.3)
Gastritis	0.365	0	0	1 (0.8)	1 (0.3)
Intestinal fistula	0.365	1 (0.8)	0	0	1 (0.3)
Intestinal obstruction	0.370	0	1 (0.8)	0	1 (0.3)
Localized intraabdominal fluid collection	0.365	0	0	1 (0.8)	1 (0.3)
Nausea	0.136	0	2 (1.6)	0	2 (0.5)
Small intestinal obstruction	0.606	0	1 (0.8)	1 (0.8)	2 (0.5)
Vomiting	0.370	0	1 (0.8)	0	1 (0.3)
General disorders and administration site conditions	0.442	1 (0.8)	1 (0.8)	3 (2.4)	5 (1.3)
Death	0.365	0	0	1 (0.8)	1 (0.3)
Hernia	0.365	0	0	1 (0.8)	1 (0.3)
Pyrexia	0.365	1 (0.8)	0	0	1 (0.3)
Wound necrosis	0.606	0	1 (0.8)	1 (0.8)	2 (0.5)
Hepatobiliary disorders	0.602	1 (0.8)	0	1 (0.8	2 (0.5)
Cholelithiasis	0.365	1 (0.8)	0	0	1 (0.3)
Jaundice cholestatic	0.365	0	0	1 (0.8)	1 (0.3)
Infections and infestations	0.288	9 (7.3)	4 (3.2)	5 (4.0)	18 (4.8)
Bacteraemia	0.370	0	1 (0.8)	0	1 (0.3)
Cellulitis	0.365	0	0	1 (0.8)	1 (0.3)
Device related infection	0.365	1 (0.8)	0	0	1 (0.3)
Gastroenteritis	0.365	1 (0.8)	0	0	1 (0.3)
Incision site infection	0.365	1 (0.8)	0	0	1 (0.3)

Table 9. Number (%) of Subjects Reporting Serious Adverse Events - Safety Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total N=373
		MOA-728 12 mg n=124	MOA-728 24 mg n=125	Placebo n=124	
Klebsiella bacteraemia	0.365	0	0	1 (0.8)	1 (0.3)
Pneumonia	0.370	0	1 (0.8)	0	1 (0.3)
Post procedural infection	0.365	0	0	1 (0.8)	1 (0.3)
Urinary tract infection	0.365	1 (0.8)	0	0	1 (0.3)
Wound infection	0.062	5 (4.0)	0	2 (1.6)	7 (1.9)
Wound infection staphylococcal	0.368	1 (0.8)	2 (1.6)	0	3 (0.8)
Injury, poisoning and procedural complications	0.442	5 (4.0)	4 (3.2)	8 (6.5)	17 (4.6)
Incisional hernia, obstructive	0.370	0	1 (0.8)	0	1 (0.3)
Postoperative ileus	0.597	3 (2.4)	1 (0.8)	2 (1.6)	6 (1.6)
Postoperative wound implication	0.606	1 (0.8)	1 (0.8)	0	2 (0.5)
Seroma	0.364	0	1 (0.8)	2 (1.6)	3 (0.8)
Wound dehiscence	0.048*	0	0	3 (2.4)	3 (0.8)
Wound secretion	0.602	1 (0.8)	0	1 (0.8)	2 (0.5)
Investigations	0.606	0	1 (0.8)	1 (0.8)	2 (0.5)
Liver function test abnormal	0.606	0	1 (0.8)	1 (0.8)	2 (0.5)
Metabolism and nutrition disorders	0.365	1 (0.8)	0	0	1 (0.3)
Dehydration	0.365	1 (0.8)	0	0	1 (0.3)
Nervous system disorders	0.365	0	0	1 (0.8)	1 (0.3)
Transient ischaemic attack	0.365	0	0	1 (0.8)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0.705	3 (2.4)	2 (1.6)	4 (3.2)	9 (2.4)
Atelectasis	0.602	1 (0.8)	0	1 (0.8)	2 (0.5)
Dyspnoea	0.370	0	1 (0.8)	0	1 (0.3)
Pneumonia aspiration	0.365	1 (0.8)	0	0	1 (0.3)
Pulmonary embolism	0.364	0	1 (0.8)	2 (1.6)	3 (0.8)
Pulmonary oedema	0.365	0	0	1 (0.8)	1 (0.3)
Respiratory failure	0.365	1 (0.8)	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	0.365	1 (0.8)	0	0	1 (0.3)
Skin necrosis	0.365	1 (0.8)	0	0	1 (0.3)
Vascular disorders	0.602	1 (0.8)	0	1 (0.8)	2 (0.5)
Deep vein thrombosis	0.365	0	0	1 (0.8)	1 (0.3)
Hypotension	0.365	1 (0.8)	0	0	1 (0.3)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall P-value: Refers to No. of Subjects data. P-value for Chi-Square.
MOA-728 = methylnaltrexone; N = total number of subjects; n = number of subjects in each treatment group; No = number.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
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 ≥2 different adverse events within the higher level category.

Discontinuations due to Adverse Events: A total of 19 (5.1%) subjects withdrew from the study because of AEs (6 subjects [4.8%] in the IV MOA-728 12 mg treatment group, 8 [6.4%] in the IV MOA-728 24 mg treatment group, and 5 [4.0%] in the placebo group). The AEs leading to discontinuation were:

MOA-728 12 mg group: Abdominal pain, abdominal pain upper, constipation, postoperative ileus, dyspepsia, hypotension.

MOA-728 24 mg group: Abdominal pain, constipation, chest pain and anxiety, postoperative ileus, headache, tachycardia, dyspnea and pneumonia, liver function test abnormal.

Placebo group: Wound dehiscence, headache, transient ischemic attack, death, and diarrhea.

Deaths: One (1) subject died during the study. A 64-year-old man in the placebo group died on study Day 4 from unknown causes. The death was considered by the Investigator as not related to the test article.

Clinical Laboratory Test Results: A total of 41 (11.0%) subjects had potentially clinically important (PCI) laboratory test results (13 subjects [10.5%] in the IV MOA-728 12 mg treatment group, 14 [11.2%] in the IV MOA-728 24 mg treatment group, and 14 [11.3%] in the placebo group). There were no statistically significant differences observed between the treatment groups (p=1.000). The most frequent PCI laboratory test results (≥1% in any treatment group) were low lymphocyte count (9 subjects [2.4%]; 4 [3.2%] in the IV MOA-728 12 mg treatment group, 1 [0.8%] in the IV MOA-728 24 mg treatment group, and 4 [3.2%] in the placebo group), high glucose concentration (fasting) (4 subjects [2.0%]; 3 [4.8%] in the IV MOA-728 24 mg treatment group and 1 [1.4%] in the placebo group), high glucose concentration (nonfasting) (5 subjects [1.5%]; 3 [2.7%] in the IV MOA-728 24 mg treatment group and 2 [1.9%] in the placebo group), low potassium concentration (5 subjects [1.3%]; 1 [0.8%] in the IV MOA-728 12 mg treatment group, 3 [2.4%] in the IV MOA-728 24 mg treatment group, and 1 [0.8%] in the placebo group), low albumin concentration (5 subjects [1.3%]; 3 [2.4%] in the IV MOA-728 12 mg treatment group, 1 [0.8%] in the IV MOA-728 24 mg treatment group, and 1 [0.8%] in the placebo group), and high total bilirubin concentration (4 subjects [1.1%]; 1 [0.8%] in the IV MOA-728 12 mg treatment group, 1 [0.8%] in the IV MOA-728 24 mg treatment group, and 2 [1.6%] in the placebo group).

Vital Signs: Overall, a review of vital signs measurements revealed a higher incidence of PCI increases in pulse (≥120 bpm) and a mean increase in pulse (post relative to preinfusion) for the IV MOA-728 12 mg treatment group. In the IV MOA-728 12 mg treatment group, significant decreases from baseline in adjusted mean value for pulse (≥120 bpm) in the range of -0.55 to 20.20 bpm (p>0.01) were observed. The number of subjects with PCI increases in pulse (≥120 bpm) measurement were significantly different (p=0.007) (0 subjects in the IV MOA-728 12 mg treatment group, 3 [2.4%] in the IV MOA-728 24 mg treatment group, and 8 [6.5%] in the placebo group) among the treatment groups. The number of subjects with PCI decreases in supine systolic blood pressure measurements were not significantly different between the treatment groups (p=0.237) (19 subjects [5.2%]; 7 [5.7%] in the

IV MOA-728 12 mg treatment group, 9 [7.3%] in the IV MOA-728 24 mg treatment group, and 3 [2.5%] in the placebo group).

Electrocardiogram: A total of 244 (65.9%) subjects had PCI changes in ECG readings (73 subjects [59.3%] in the IV MOA-728 12 mg treatment group, 91 [74.0%] in the IV MOA-728 24 mg treatment group, and 80 [64.5%] in the placebo group. The differences in PCI changes in ECG readings among the treatment groups were significant at the 0.05 level of statistical significance (p=0.047). The most frequent PCI changes in ECG readings (≥10% in any treatment group) were heart rate ≤50 beats/min (30 subjects [8.1%]; 5 [4.1%] in the IV MOA-728 12 mg treatment group, 17 [13.8%] in the IV MOA-728 24 mg treatment group, and 8 [6.5%] in the placebo group [p=0.018]), rhythm (not sinus rhythm) (8 subjects [7.4%]; 1 [4.2%] in the IV MOA-728 12 mg treatment group, 5 [10.9%] in the IV MOA-728 24 mg treatment group, and 2 [5.3%] in the placebo group), PR interval ≥200 ms (48 subjects [13.0%]; 17 [13.8%] in the IV MOA-728 12 mg treatment group, 15 [12.3%] in the IV MOA-728 24 mg treatment group, and 16 [13.0%] in the placebo group). On Day 1 after surgery, the PCI heart rate (≤50 beats/min) was not significantly different between the treatment groups (p=0.619) (10 subjects [2.7%]; 3 [2.4%] in the 12 mg treatment group, 5 [4.1%] in the 24 mg treatment group, and 2 [1.6%] in the placebo group).

CONCLUSIONS: This study was designed to assess the efficacy of IV MOA-728 in subjects who had undergone repair of large (≥10 cm) ventral hernias, with or without a mesh prosthesis via laparotomy or laparoscopy. The efficacy analyses show that there were no statistically significant differences observed in either of the IV MOA-728 treatment groups when compared with the placebo control group.

The safety results show that IV MOA-728 was safe and well tolerated when administered IV at the 12 mg and 24 mg dose levels. A total of 65 (17.4%) subjects had SAEs during the study, including 20 (16.1%) in the IV MOA-728 12 mg treatment group, 17 (13.6%) in the IV MOA-728 24 mg treatment group, and 28 (22.6%) in the placebo group. One (1) subject died during the study from unknown causes and the death was considered not related to the test article. A total of 286 (76.7%) subjects had ≥1 TEAEs (90 [72.6%] in the IV MOA-728 12 mg treatment group, 97 [77.6%] in the IV MOA-728 24 mg treatment group, and 99 [79.8%] in the placebo group). There were no statistically significant differences among the treatment groups in the overall occurrence of TEAEs (p=0.384). The most frequent TEAEs (≥5% in any treatment group) were nausea (112 subjects [30.0%], vomiting (58 subjects [15.5%], pyrexia (51 subjects [13.7%]), pruritus (45 subjects [12.1%]), constipation (34 subjects [9.1%]), urinary retention (33 subjects [8.8%]), headache (30 subjects [8.0%]), hypertension (19 subjects [5.1%]), hypokalemia (18 subjects [4.8%]), dizziness (16 subjects [4.3%]), tachycardia (16 subjects [4.3%]), somnolence (14 subjects [3.8%]), dyspnea (13 [3.5%]), and fatigue (11 subjects [2.9%]). There were no clinically meaningful changes in laboratory test results, vital signs measurements, or ECG readings.