This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Synopsis

Identifier: RM2006/00303/00 **Study Number:** SB-767905/013

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study to Evaluate the Efficacy and Safety of Alvimopan 0.5mg Once Daily and 0.5mg Twice Daily for 12 Weeks for the Treatment of Opioid-Induced Bowel Dysfunction in Adults taking Opioid Therapy for Persistent Non-Cancer Pain

Investigators: Multicenter study.

Study centers: A total of 153 centers enrolled subjects for this multicenter study sponsored by GlaxoSmithKline (GSK): 109 in North America (99 in the United States [US], 10 in Canada), 27 in Europe (4 in France, 4 in Norway, 4 in Sweden, 2 in Switzerland, 5 in the Netherlands, 4 in Spain, and 4 in Hungary), and 17 in International countries (10 in Australia, 3 in New Zealand, and 4 in South Africa).

Publication(s): None at the time of this report.

Study Period: 29 August 2005 (first subject screened) - 29 June 2006 (last subject completed)

Phase of Development: III

Objectives: The primary objective of this study was to compare alvimopan with placebo for efficacy in the treatment of opioid-induced bowel dysfunction (OBD). The secondary objectives were to: compare alvimopan with placebo for safety and tolerability; compare alvimopan with placebo for effects on opioid analgesia; compare alvimopan with placebo for constipation-related quality of life; and explore the relationship between genetic variants and 1) the safety and/or tolerability of alvimopan, and 2) the efficacy of alvimopan.

Methodology: This was a Phase III, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of oral alvimopan 0.5mg once daily and 0.5mg twice daily administered to adult subjects experiencing OBD as a result of taking chronic opioid therapy for persistent non-cancer pain. The study consisted of a 2-week baseline period, a 12-week treatment period, and a 2-week post-treatment follow-up period. Clinic visits were conducted at Screen, Day 1/Randomization, Weeks 4, 8, and 12, and 2 weeks after investigational product had been discontinued. An Interactive Voice Response System (IVRS) was used for daily collection of bowel movement (BM) frequency, daily subjective lower (straining, incomplete evacuation, stool consistency) and upper (abdominal bloating, abdominal pain, and decreased appetite) gastrointestinal (GI) symptom ratings, daily rescue laxative use, daily opioid concomitant medications, weekly pain intensity ratings, and weekly OBD symptoms improvement scale (OBD SIS) ratings. All other assessments were conducted at the clinic visits.

Number of subjects: Recruitment was planned for 480 subjects, 160 per treatment arm. A total of 485 subjects were randomized.

Number of Subjects	Placebo	Alvimopan 0.5mg QD	Alvimopan 0.5mg BID
Planned, N	160	160	160
Randomized, N	164	161	160
Completed, n (%)	131 (80)	128 (80)	121 (76)
Total Withdrawn, n (%)	33 (20)	33 (20)	39 (24)
Withdrawn due to adverse events	12 (7)	12 (7)	15 (9)
Withdrawn due to lack of efficacy	4 (2)	2 (1)	5 (3)
Withdrawn for other reasons	17 (10)	19 (12)	19 (12)

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥18 years who were on stable daily doses of opioids of at least 30mg oral morphine equivalents for at least one month for persistent non-cancer pain and experiencing protocol-defined OBD were enrolled.

Treatment administration: Investigational product was supplied as capsules containing alvimopan 0.5mg (Batch # [redacted] and placebo (excipient only) (Batch #s [redacted] Subjects were randomized 1:1:1 to receive one of the following treatments:

Treatment Group	Morning Capsule	Evening Capsule
Placebo	Placebo	Placebo
Alvimopan 0.5mg QD	Alvimopan 0.5mg	Placebo
Alvimopan 0.5mg BID	Alvimopan 0.5mg	Alvimopan 0.5mg

Criteria for evaluation: The primary efficacy endpoint was the proportion of subjects responding on spontaneous bowel movement (SBM) frequency. SBMs were BMs with no laxative use in the previous 24 hours. A responder was a subject that reported an average of ≥3 SBMs/week and had an average increase from baseline of ≥1 SBM/week over the Treatment Period. Secondary efficacy endpoints were:

- Proportion of subjects responding on the OBD Symptoms Improvement Scale (OBD SIS). Using a 7-point Likert scale, a responder was defined as a subject with an OBD score of 6 (moderately improved) or 7 (substantially improved).
- Proportion of subjects responding (as defined in Section 5.8.8.2 and Section 5.8.8.3) on BM symptoms (incomplete evacuation, stool consistency, and straining) and related abdominal symptoms (abdominal bloating, abdominal pain, and decreased appetite).

Safety endpoints included incidence of adverse events (AEs), clinical laboratory (hematology and clinical chemistry) analysis, vital signs, changes in weekly pain intensity scores, and morphine-equivalents of opioid used.

Health outcomes measures included changes in patient assessment of constipation-specific quality of life questionnaire (PAC-QOL) total scores and subscale scores.

Statistical methods: A sample size of 160 subjects per treatment group, was chosen to provide 93% power at the two-sided α=0.05 significance level to detect a 20% difference in treatment for a total of 480 subjects. This target sample size would also provide 50% power to detect treatment differences as small as 12% at the α=0.05 level. The Intent-to-Treat (ITT) Population (all subjects randomized) was used for efficacy and health outcomes analyses. The Safety Population (all subjects randomized who received at least one dose of investigational product) was used for all safety analyses.

The primary timepoint for assessing all endpoints was the average over the 12-week treatment period, and if significance was demonstrated for this interval, the individual weekly assessments were then examined for significance after adjustment for multiplicity using Hommel's general multiple Simes procedure. Missing data were handled according to the last observation carried forward (LOCF) principle. The LOCF data were the primary data set for the efficacy analyses.

The primary comparison of interest was the comparison between alvimopan 0.5mg twice daily and placebo for the proportion of SBM frequency responders (subjects reporting an average of ≥3 SBMs/week and an increase from baseline of ≥1 SBM/week) with significance interpreted at the 0.05 significance level. Other comparisons of interest included comparisons between alvimopan 0.5mg once daily and placebo for the proportion of SBM frequency responders and between each alvimopan dose and placebo for OBD SIS, stool consistency, straining, incomplete evacuation, abdominal bloating, abdominal pain, and decreased appetite.

The efficacy endpoints were divided into three groups of hypotheses for hierarchical evaluation based on closed testing procedure for composite hypotheses with a parallel gate-keeping structure with two parallel pre-specified sequences of composite hypotheses for the interpretation of statistical significance. This procedure controlled the experimental error at the 0.05 significance level for all composite groups.

AEs were classified by body system and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term and were tabulated by treatment group, maximum intensity, seriousness, and attribution to study drug. Comparison of the incidence of AEs for each alvimopan treatment group versus placebo were made using Fishers exact test. Pairwise comparisons of each alvimopan group with placebo for subjects with abnormal or beyond threshold laboratory values at baseline and for transitions from baseline were made using Fisher's exact test.

Pairwise comparisons for change from baseline between each alvimopan dose group versus placebo were made for pain intensity ratings, opioid consumption in morphine equivalent total daily dose (METDD), and the health outcomes PAC-QOL total and subscale scores using Wilcoxon rank sum tests.

Summary:

Demographics: Baseline demography and opioid use were similar across the treatment groups. The majority of subjects were White, female, and <65 years of age. Average duration of pain condition was 9.9 years. Average chronic opioid use was about 7.0 years and duration of current opioid therapy was approximately 2.8 years.

Demographic	Placebo N=164	Alvimopan 0.5mg QD N=161	Alvimopan 0.5mg BID N=160
Sex, n (%)			
Male	61 (37)	50 (31)	64 (40)
Female	103 (63)	111 (69)	96 (60)
Age, yr			
Mean (SD)	52.3 (11.5)	51.2 (11.6)	53.0 (11.7)
Race, n (%)			
White	144 (88)	150 (93)	149 (93)
Duration of pain condition, yr			
Mean (SD)	11.0 (9.8)	8.6 (7.7)	10.0 (8.8)
Opioid Use, yr			
Chronic, mean (SD)	7.9 (7.3)	6.3 (6.3)	6.8 (6.5)
Current, mean (SD)	2.8 (3.2)	2.6 (3.1)	2.9 (3.6)

Efficacy: There were greater proportions of SBM responders in both alvimopan treatment groups compared with placebo, although differences were not statistically significant.

Primary Efficacy Endpoint

SBM frequency responders over the 12-week treatment period	Placebo N=164	Alvimopan 0.5mg QD N=161	Alvimopan 0.5mg BID N=160
Responders, n (%)	92 (56)	100 (63)	101 (63)
95% CI	(48.50, 63.69)	(55.00, 70.00)	(55.65, 70.60)
Treatment difference, %	---	6.40	7.03
95% CI (Tmt diff)	---	(-4.27, 17.08)	(-3.63, 17.68)
p-value[1]	---	0.259	0.214

1. Fisher's exact test vs. placebo. Significance between alvimopan 0.5mg BID and placebo is 0.05, significance between alvimopan 0.5mg QD and placebo is 0.01.

The proportion of weeks in which subjects reported either moderate or substantial improvement in their OBD symptoms, based on the OBD Symptoms Improvement Scale, was higher in both the alvimopan 0.5mg QD (37.0%; p=0.004) and the alvimopan 0.5mg BID (35.3%; p=0.012) groups, compared with placebo (23.1%).

Among lower GI symptoms, a higher proportion (>10%) of subjects in the alvimopan 0.5mg QD group achieved improvement in straining compared with placebo; a higher proportion of subjects in the alvimopan 0.5mg BID group also achieved improvement in stool consistency compared with placebo. All other differences in lower GI symptoms (incomplete evacuation in both groups, stool consistency in the alvimopan 0.5mg QD group, and straining in the alvimopan 0.5mg BID group) were <10% between the alvimopan and placebo groups.

No differences between alvimopan and placebo in the upper GI symptoms of abdominal bloating, abdominal pain, or decreased appetite were >10%.

Safety: The majority of subjects were exposed to investigational product for between 78 and 91 days. There were no statistically significant differences between either dose of alvimopan and placebo in the overall incidence of AEs. GI-related AEs occurred most often (22% placebo group, 33% alvimopan 0.5mg QD group, and 25% alvimopan 0.5mg BID group).

Most Common Adverse Events

	Number (%) of Subjects		
Adverse Event (Preferred Term)	Placebo N=164	Alvimopan 0.5mg QD N=161	Alvimopan 0.5mg BID N=160
Any AE	88 (54)	101 (63)	88 (55)
Abdominal pain	14 (9)	26 (16)	19 (12)
Headache	8 (5)	18 (11)	12 (8)
Diarrhea	9 (5)	12 (7)	8 (5)
Nausea	7 (4)	9 (6)	10 (6)
Vomiting	6 (4)	6 (4)	9 (6)
Nasopharyngitis	4 (2)	7 (4)	6 (4)
Back pain	6 (4)	2 (1)	7 (4)
Flatulence	4 (2)	6 (4)	3 (2)
Influenza	2 (1)	5 (3)	6 (4)
Sinusitis	3 (2)	5 (3)	3 (2)
Abdominal distension	3 (2)	2 (1)	5 (3)
Upper respiratory tract infection	4 (2)	6 (4)	0
Pharyngolaryngeal pain	5 (3)	1 (<1)	3 (2)
Pyrexia	4 (2)	1 (<1)	3 (2)
Cough	2 (1)	1 (<1)	4 (3)
Sinus congestion	4 (2)	0	2 (1)
Fatigue	5 (3)	1 (<1)	0
Hypertension	4 (2)	1 (<1)	1 (<1)

No deaths were reported during the study. There were no statistically significant differences between either dose of alvimopan and placebo in the overall percentages of subjects with serious adverse events (SAEs) (7% placebo group, 7% alvimopan 0.5mg QD group, and 6% alvimopan 0.5mg BID group). Likewise, there were no statistically significant differences between either dose of alvimopan and placebo in the overall percentages of subjects who withdrew due to AEs (7% placebo, 7% alvimopan 0.5mg QD group, and 9% alvimopan 0.5mg BID group).

Pain intensity diminished slightly in all three treatment groups during treatment compared with baseline, indicating that alvimopan treatment does not antagonize opioid analgesia. Opioid consumption remained stable for each treatment group during the treatment and follow-up periods and fluctuated by approximately the same amount across

treatment groups, suggesting that that subjects felt no need to increase their opioid use and providing further evidence that alvimopan treatment does not antagonize opioid analgesia.

No notable differences were observed between either dose of alvimopan and placebo with regard to shifts in clinical laboratory parameters. No clinically important differences were seen with respect to changes from baseline in any vital signs parameter.

Pharmacogenetics: No pharmacogenetic analyses were conducted for this study.

Health Outcomes: Alvimopan 0.5mg QD was associated with a greater improvement in the Physical Discomfort subscale relative to placebo at Week 12. No other differences were observed between the alvimopan and placebo treatment groups at Week 12.

Conclusions: The inability of Study 013 to achieve statistical significance on the primary endpoint was due to an unusual and inexplicably high placebo response observed during Weeks 5-7 and 10-12. Examination of the dataset and study conduct failed to uncover the reason for this effect. Therefore it appears that the failure of Study 013 was related to a small but known chance (~7%) of not detecting a difference.

Although additional endpoints were not formally subjected to statistical testing under the closed testing procedure, these results provide additional evidence relevant to the efficacy and safety of alvimopan:

- Alvimopan treatment was associated with a greater change in bowel movements without the use of laxatives, as well as spontaneous complete bowel movements, over the 12-week study period relative to placebo.
- Alvimopan treatment was superior to placebo for the proportion of weeks OBD symptoms were moderately or substantially improved.
- Alvimopan was well-tolerated, with a tolerability profile similar to placebo.
- Withdrawal rates for AEs were low for both alvimopan regimens and similar to placebo.
- There was no evidence that alvimopan antagonized opioid analgesia.

Date of Report: 18 June 2007