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: ZM2006/00094/00 **Study Number:** SB-767905/014

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study to Evaluate the Long-Term Safety of Alvimopan 0.5mg Twice Daily for the Treatment of Opiod-Induced Bowel Dysfunction in Adults Taking Opioid Therapy for Persistent Non-Cancer Pain.

Investigator(s): Multicenter study.

Study center(s): A total of 229 centers enrolled subjects for this multicenter study sponsored by GlaxoSmithKline (GSK): 187 in North America (162 in the United States [US] and 25 in Canada), 24 in Europe (1 in Austria, 1 in Denmark, 1 in Finland, 1 in Hungary, 2 in the Netherlands, 3 in Poland, 4 in Spain, 4 in Sweden, 1 in Switzerland, and 6 in the United Kingdom [UK]), and 18 in International countries (9 in Australia, 4 in Hong Kong, 3 in New Zealand, and 2 in Taiwan).

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

Study Period: 29 August 2005 (first subject screened) to 16 February 2007 (last subject completed)

Phase of Development: III

Objectives: The primary objective of this study was to compare the long-term safety and tolerability of twice daily dosing of alvimopan (0.5mg) with that of placebo, in subjects with opioid-induced bowel dysfunction (OBD). The secondary objectives were to compare alvimopan with placebo for constipation-related quality of life, to describe the population pharmacokinetics of alvimopan and its main metabolite (SB-791399), and to explore the relationship between genetic variants and 1) the safety and/or tolerability of alvimopan and 2) the pharmacokinetics of alvimopan and its main metabolite.

Methodology: This was a 12-month Phase III, randomized, double-blind, placebo controlled parallel group multicenter safety study to compare the safety and tolerability of oral alvimopan 0.5mg twice daily treatment with that of placebo in adult subjects experiencing OBD as a result of chronic opioid use for persistent non-cancer pain. The study consisted of a one-week Screening period, a 12-month Treatment period, and a 2-week post-treatment Follow-up period. Subjects kept a daily paper drug record of all medications taken. Safety assessments, health outcomes assessments and investigational product assessments were carried out at the scheduled clinic visits (Screening, Randomization, Month 1, 3, 9 and 12 Visits, and Follow-up).

Number of subjects: Recruitment was planned for 750 subjects. Subjects were randomized 2:1 to alvimopan:placebo treatment. A total of 805 subjects were randomized.

Number of Subjects	Placebo	Alvimopan 0.5mg BID
Planned, N	250	500
Randomized, N	267	538
Completed, n (%)	131 (49)	291 (54)
Total Withdrawn, n (%)	136 (51)	247 (46)
Withdrawn due to adverse events, n (%)	32 (12)	85 (16)
Withdrawn for other reasons, n (%)	104 (39)	162 (30)

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 and placebo (excipient only). Subjects were randomized 2:1 to receive alvimopan 0.5mg or placebo twice daily.

Criteria for evaluation: The primary endpoint was the incidence of reported clinical adverse events. Other safety endpoints included changes in clinical laboratory analytes, pain intensity scores, morphine-equivalents of opioid use, constipation-specific quality of life, and plasma concentrations of alvimopan and its main metabolite.

Statistical methods: A target sample size of 750 subjects was chosen to provide 94% power to detect a 10% increase over placebo in adverse events occurring with a 10% incidence in the placebo group. In addition, the sample size provided 90% power at the two-sided α=0.05 significance level to detect differences of at least 1 point on the 5-point patient assessment of constipation quality of life (PAC-QOL) rating scale assuming a standard deviation of 4 points.

Adverse events (AEs) were classified by system organ class (SOC) using the Medical Dictionary for Regulatory Affairs (MedDRA) preferred term and were tabulated by treatment group, maximum intensity, seriousness, and attribution to study drug. The incidence of AEs and the number of subjects with abnormal or beyond threshold laboratory values at baseline were compared between the alvimopan and placebo group using Fisher's exact test.

Pairwise comparisons for change from baseline between the alvimopan and placebo group 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.

An unblinded interim analysis of safety data was performed after all subjects had been enrolled in the study for at least 6 months.

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 10.6 years. Average chronic opioid use was approximately 7.6 years and duration of current opioid therapy was approximately 3.0 years.

Demographic	Placebo N=267	Alvimopan 0.5mg BID N=538
Sex, n (%)		
Male	100 (37)	188 (35)
Female	167 (63)	350 (65)
Age, year		
Mean (SD)	51.9 (12.2)	53.8 (12.9)
Race, n (%)		
White	233 (87)	492 (91)
Duration of pain condition, year		
Mean, (SD)	10.0 (8.7)	10.9 (9.5)
Opioid Use, year		
Chronic, mean (SD)	7.6 (7.2)	7.5 (7.1)
Current, mean (SD)	3.1 (3.6)	3.0 (3.3)

Safety: The majority of subjects were exposed to investigational product for at least 331 days. There was a statistically significant difference between alvimopan and placebo treatment in the overall incidence of AEs (p=0.047). Gastrointestinal (GI)-related AEs occurred most often (35% placebo group and 40% alvimopan 0.5mg twice daily [BID] group).

Most Common Adverse Events (Preferred Term)	Number (%) of Subjects	
	Placebo N=267	Alvimopan 0.5mg BID N=538
Any AE	189 (71)	416 (77)
Abdominal pain	36 (13)	85 (16)
Diarrhea	32 (12)	76 (14)
Headache	30 (11)	53 (10)
Nausea	29 (11)	49 (9)
Vomiting	17 (6)	35 (7)
Back pain	19 (7)	30 (6)
Sinusitis	19 (7)	30 (6)
Upper respiratory tract infection	13 (5)	32 (6)
Urinary tract infection	9 (3)	25 (5)
Arthralgia	14 (5)	20 (4)
Nasopharyngitis	15 (6)	19 (4)
Insomnia	7 (3)	22 (4)

Four deaths (two in the placebo group and two in the alvimopan group) occurred during this study. The deaths in the placebo group were attributed to metastatic prostate cancer in one subject and accidental methadone overdose in the other subject. The deaths in the alvimopan group were attributed to acute myocardial infarction in one subject and pneumonia, acute respiratory distress, sepsis, and septic shock in the other subject. In each case, the investigator assessed the events as not related to the investigational product.

There was no statistically significant difference between alvimopan 0.5mg BID and placebo in the overall percentage of subjects with serious adverse events (SAEs) (11% placebo and 13% alvimopan 0.5mg BID). Likewise, there was no statistically significant difference between alvimopan 0.5mg BID and placebo in the overall percentages of subjects who withdrew due to AEs (12% placebo and 16% alvimopan 0.5mg BID).

A numerical increase in the incidence of myocardial infarctions and other serious cardiovascular adverse events in alvimopan-treated subjects was identified while the study was ongoing. As a result, an Independent Data Monitoring Committee (IDMC) was established for the review of cardiovascular adverse events and to make recommendations for the protection of subjects. However, the observed treatment differences in cardiovascular events were not statistically significant and may be the result of a chance finding, stemming from a comparison of a small total number of events in a study not designed to make formal assessments of cardiovascular safety.

Analyses of the frequency of adverse events also showed a numerical imbalance in reports of benign and malignant neoplasms in the alvimopan treatment arm as well as an increase in the reports of bone fractures in subjects receiving alvimopan. The underlying cause of these imbalances is uncertain. Assessment of these events are further complicated by the fact that the number of events reported is small, as is the total population size relative to the sample size needed to accurately assess the risk for these events.

For neoplasms, careful inspection of the malignant events raise doubts as to whether an imbalance exists, as the inclusion of an additional malignant neoplasm reported in the placebo group following completion of the study and the exclusion of pre-existing or undocumented malignancies results in a distribution of cases entirely consistent with a chance allocation. Review of the imbalance in benign lesions demonstrates that these lesions were truly benign, and for the most part of minimal clinical significance.

With respect to bone fractures, the available data suggest the increased number of reports in subjects treated with alvimopan may well be related to an increased number of risk factors in these subjects for bone fragility, which predisposed to fracturing with minor trauma.

Pain intensity diminished slightly in both treatment groups during treatment compared with baseline, suggesting that alvimopan treatment does not antagonize opioid analgesia. Mean opioid consumption increased slightly from Baseline in the alvimopan 0.5mg BID group, but this difference was small relative to the overall daily opioid dose and was not clinically meaningful.

Eight subjects had ALT values which exceeded the threshold range in the alvimopan group, while no such elevations were seen with placebo. These were mostly low grade elevations that reverted to normal. None of these elevations was reported as an SAE, or accompanied by an increase in bilirubin. No clinically important differences were seen with respect to changes from baseline in any vital signs parameter.

Health Outcomes: Alvimopan 0.5mg administered twice daily for up to 12 months was associated with statistically significant improvements both in the overall PAC-QOL score and in the scores of three of the four subscales, compared with placebo.

Pharmacokinetics: Concentrations of alvimopan and SB791399 were as expected. Concentrations of SB791399 did not increase with time and remained relatively stable (with random variability) over 12 months. The majority of concentrations for those subjects experiencing any of the AEs of interest (e.g., cardiovascular [CV] SAEs, neoplasms, bone fractures, musculoskeletal pain, and abdominal pain) were within the concentrations predicted for a given dose.

Conclusions:

- Subjects treated with alvimopan 0.5mg BID reported a 6% greater incidence of AEs than placebo-treated subjects (p=0.047); the difference was driven by more GI events being reported with alvimopan which was expected and consistent with the drug's mechanism of action.
- Withdrawal rates for AEs were not significantly different between the placebo (12%) and alvimopan (16%) groups.
- There was no evidence that alvimopan antagonized opioid analgesia.
- Increased frequencies of serious CV AEs, neoplasms, and bone fractures in alvimopan-treated subjects prompted further investigation of these findings; however, it remains unclear whether a relationship exists between alvimopan exposure and increased risk of any of these adverse events.
- AEs of interest (e.g., CV AEs, neoplasms, bone fractures, musculoskeletal pain, and abdominal pain) were not explained by higher exposure to alvimopan or metabolite.
- Alvimopan was associated with improvements in overall constipation-related quality of life (PAC-QOL) as well as in the physical discomfort, worries and concerns, and dissatisfaction subscales.

Date of Report: 01 October 2007