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: RM2006/00216/00 **Study Number:** SB-767905/008

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase IIb Study to Evaluate the Efficacy and Safety of Multiple Alvimopan Dosage Regimens for the Treatment of Opioid-Induced Bowel Dysfunction in Cancer Pain Subjects

Investigators: Multicenter study.

Study centers: A total of 80 centers enrolled subjects for this multicenter study sponsored by GlaxoSmithKline (GSK): 33 in North America (30 in the United States [US] and three in Canada), 25 in Europe (five in Italy, five in Spain, three in France, three in Hungary, three in Portugal, two in the United Kingdom (UK), one each in the Netherlands, Finland, Poland, and Germany), four in Asia (one in Hong Kong, one in the Philippines, one in Taiwan, and one in Thailand), three in South America (two in Argentina and one in Peru), and 15 in International countries (three in the Russian Federation, three in the Czech Republic, three in New Zealand, two in South Africa, two in Australia, one in Pakistan, and one in India).

Publications: None at the time of this report.

Study Period: 08 October 2003 (first subject screened) - 09 May 2006 (last subject completed)

Phase of Development: IIB

Objectives: The primary objective of this study was to identify at least one alvimopan treatment regimen that improved spontaneous complete bowel movement (SCBM) frequency compared with placebo, while maintaining an acceptable tolerability profile. Secondary objectives were to further compare the efficacy and safety among treatment regimens and to demonstrate the lack of effect of the treatment regimens on opioid analgesia.

Methodology: This was a multicenter, randomized, double-blind, placebo controlled, parallel group study to evaluate the efficacy and safety of alvimopan in adults experiencing OBD as a result of chronic opioid therapy for cancer pain. The original study design had four treatment arms: alvimopan 0.5mg twice daily (BID), alvimopan 1mg once daily (QD), alvimopan 1mg BID and placebo. The study originally consisted of a 1-week baseline period, a 6-week treatment period and a 2-week post-treatment follow-up period. A Daily Diary was used for daily collection of bowel movement (BM) frequency, daily subjective BM symptom ratings (incomplete evacuation, stool consistency, and straining), daily rescue laxative use, weekly pain intensity ratings, and some OBD global improvement assessments. All other assessments were conducted at the clinic visits. The original primary endpoint was to identify at least one alvimopan treatment regimen that improves spontaneous bowel movement (SBM) frequency compared to placebo while maintaining an acceptable tolerability profile.

Several study design changes were implemented per Protocol Amendments 4 and 5 due to impediments to enrollment identified by investigators. The revisions were intended to reduce the burden on cancer subjects, particularly those who were very ill or incapacitated, while maintaining the validity of the study. Key changes included:

- Revised OBD definition to be based on <3 SCBMs per week rather than <3 spontaneous BMs (SBMs),
- Revised primary endpoint from SBMs to SCBMs to be aligned with the cancer population with subsequent recalculation of the sample size,
- Shortened the treatment period to 3 weeks and follow-up period to 1 week, removed one study visit, permitted the clinic visits to be conducted in the home or hospice setting, and converted the Follow-up Visit to a telephone contact,
- Converted daily data collection from a telephonic interactive voice response system (IVRS) to a paper diary, and
- Reduced the number of blood samples (eliminated PK and pharmacogenetic blood draws) and subject completed questionnaires by eliminating several secondary endpoints (OBD-Related Symptoms, SF-36, and PAC-QOL).

Per Protocol Amendment 5, the alvimopan 1mg QD treatment arm was dropped. Approximately 20 subjects had been randomized to this dose at the time the amendment was first approved.

Number of subjects: Recruitment was originally planned for 500 subjects, 125 per treatment arm. With the change in the primary endpoint and the curtailment of the alvimopan 1mg QD treatment arm as part of Protocol Amendment 5, the total sample size was decreased to an estimated 215 subjects.

Number of Subjects	Placebo	Alvimopan 0.5mg BID	Alvimopan 1mg QD[1]	Alvimopan 1mg BID	Total
Planned, N	65	65	65	65	260
Randomized, N	71	68	27	67	233
Completed, n (%)	57 (80)	56 (82)	19 (70)	54 (81)	186 (80)
Total withdrawn, n (%)	14 (20)	12 (18)	8 (30)	13 (19)	47 (20)
Withdrawn due to adverse events	6 (8)	6 (9)	6 (22)	9 (13)	27 (12)
Withdrawn due to lack of efficacy	3 (4)	0	0	0	3 (1)
Withdrawn for other reasons	6 (8)	9 (13)	4 (15)	8 (12)	27 (12)

1. Protocol Amendment 5 dropped the alvimopan 1mg QD treatment arm.

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥18 years with protocol-defined OBD resulting from chronic opioid treatment for cancer pain were eligible for inclusion in the study. The opioid treatment had to be dosed chronically for at least one month at a minimum daily dose of at least 30mg oral morphine equivalents and dosed in a stable fashion for a least one week without any dose reductions.

Acceptable routes of administration included enteral (oral, transmucosal, sublingual), parenteral (intravenous, subcutaneous, intramuscular), transdermal, or rectal.

Treatment administration: Investigational product was supplied as capsules containing alvimopan 0.5mg (Batch #s [redacted] alvimopan 1mg (Batch #s [redacted] and placebo (excipient only) (Batch #s [redacted] Subjects were randomized 1:1:1:1 to receive one of the following treatments for 3 weeks:

Treatment Group	Morning Capsule	Evening Capsule
Placebo	Placebo	Placebo
Alvimopan 0.5mg BID	Alvimopan 0.5mg	Alvimopan 0.5mg
Alvimopan 1mg QD[1]	Alvimopan 0.5mg for first 3 days, Alvimopan 1mg thereafter	Placebo
Alvimopan 1mg BID	Alvimopan 0.5mg for first 3 days, Alvimopan 1mg thereafter	Alvimopan 0.5mg for first 3 days, Alvimopan 1mg thereafter

1. Protocol Amendment 5 dropped the alvimopan 1mg QD treatment arm

Criteria for evaluation: The primary efficacy endpoint was changes in weekly SCBM frequency during the 3-week treatment period. A SCBM was a BM with no rescue laxative use in the previous 24 hours and that provided the subject with a feeling of complete evacuation of the rectum. The secondary efficacy endpoints were:

- Responders for OBD Global Improvement (using a 7-point Likert scale):
  1. Proportion of subjects reporting that their OBD was "moderately improved" or "substantially improved" compared with the baseline when asked at Week 3.
  2. Proportion of subjects reporting that their OBD was "moderately improved" or "substantially improved" compared with the Baseline Period when asked every week during the Treatment Period.
- Changes in weekly subjective BM symptom rating scores (incomplete evacuation, stool consistency, and straining scores).
- Changes in constipation symptom questionnaire (PAC-SYM, which assessed a total of 12 different abdominal, rectal, and stool symptoms) total scores and domain scores.
- Changes in proportion of days rescue laxatives and maintenance stool softener were used (including impact of the rescue laxative and maintenance stool softener on BM frequency, OBD Global Improvement, incomplete evacuation, stool consistency, and straining)
- Responders for Overall Satisfaction with Treatment (using a 7-point Likert scale):
  1. Proportion of subjects reporting that they are "satisfied" or "very satisfied" with their study treatment when asked at the end of treatment.

2. Proportion of subjects reporting "yes" that they would use their study treatment again when asked at the end of treatment.

- Changes in weekly BM, SBM, complete BM (CBM), and SCBM frequency
- Responders for BM frequency (including BMs, CBMs, SBMs, and SCBMs):

1. Proportion of subjects with >3 BMs/week.
2. Proportion of subjects with an increase from baseline of at least 1 BM/week.

- BM proportions analysis:

1. Proportion of days with ≥1 BM.
2. Proportion of days with ≥3 BMs.

- Maximal number of days without a BM.
- Compliance (≥80%) with investigational product.

Safety endpoints included incidence of adverse events (AEs) and treatment-limiting toxicities, clinical laboratory testing, changes in weekly pain intensity scores, oral morphine equivalents of opioids used, Modified Himmelsbach score, and vital signs. Karnofsky Performance Status was an exploratory endpoint.

Statistical methods: A sample size of 260 subjects, 65 subjects/treatment group, was chosen to provide 90% power at the two-sided α=0.05 significance level to detect an increase of 1 SCBM/week between any alvimopan group and placebo assuming a standard deviation of 1.75 SCBMs/week. Due to the curtailment of the alvimopan 1mg QD arm, the expected sample size was decreased. The three remaining arms would contribute 65 subjects each (n=195) plus approximately 20 subjects from the discontinued alvimopan 1mg QD arm for an estimated total sample size of 215.

The primary comparisons of interest were comparisons of the average weekly change in SCBM frequency during the 3-Week Treatment Period in the Intent-to-Treat (ITT) Population between the 0.5mg BID and 1mg BID alvimopan treatment groups versus placebo with adjustment for multiple comparisons using Hommel's general multiple Simes procedure. Other comparisons of interest included comparisons of each alvimopan group versus placebo for weekly changes in total BM, SBM, CBM, and SCBM frequencies, Global Improvement of OBD symptoms, changes in PAC-SYM scores, changes in weekly stool consistency and straining ratings, responders for BM (including BM, CBM, SBM, and SCBM) frequency, proportion of BMs with incomplete evacuation, the use and impact of maintenance stool softener and rescue laxatives, and overall satisfaction with treatment.

Efficacy and health outcome endpoints were divided into three groups, i.e., primary, secondary, and health outcomes, for a hierarchical and sequential evaluation of statistical significance. If the adjusted p-value for comparisons of the primary endpoint between any alvimopan group and placebo was ≤0.05, interpretation of significance proceeded to the five secondary endpoints for comparisons between that alvimopan group and placebo in the following order: global improvement of OBD symptoms, incomplete evacuation,

straining, stool consistency, and PAC-SYM. If significance was demonstrated for the global improvement of OBD symptoms, interpretation of significance proceeded to the subsequent endpoints provided significance was demonstrated for each previous endpoint.

Subsequently, if at least one of the secondary endpoints above was significant, interpretation of significance proceeded to the health outcomes endpoints in the following order: overall satisfaction with treatment at the end of the Treatment Period then willingness to use treatment at the end of the Treatment Period.

Evaluations of SBM frequency, OBD Global Improvement responders, BM scores, PAC-SYM scores, OBD-related symptom scores, rescue laxative use, proportion of days with either ≥1 or ≥3 BMs, and consecutive days with no BM in each alvimopan treatment group were compared with placebo using Wilcoxon rank sum tests. The number and proportion of responders for OBD global improvement, BM (including BM, CBM, SBM, and SCBM) frequency, overall satisfaction with treatment, and willingness to use treatment in each alvimopan group were compared with placebo using Fisher's exact test. The PAC-QOL scores were summarized using descriptive statistics.

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 Fisher's 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.

Summary:

Demographics: Baseline demography and opioid use were similar across the treatment groups. The majority of subjects were white and <65 years of age. Average duration of pain condition was 2 years. Average chronic opioid use was about 1.9 years and duration of current opioid therapy was approximately 0.8 years.

Demographics (ITT Population)	Placebo N=71	Alvimopan 0.5mg BID N=68	Alvimopan 1mg QD N=27	Alvimopan 1mg BID N=67	Total N=233
Age, yr					
Mean (SD)	59.6 (11.5)	61.0 (11.3)	60.1 (9.6)	55.3 (12.1)	58.8 (11.6)
Min-Max	32.0 - 85.0	29.0 - 85.0	39.0 - 80.0	25.0 - 81.0	25.0 - 85.0
Age range, n (%)					
<65 yr	46 (65)	42 (62)	17 (63)	53 (79)	158 (68)
≥65 yr	25 (35)	26 (38)	10 (37)	14 (21)	75 (32)
Gender, n (%)					
Female	43 (61)	40 (59)	15 (56)	39 (58)	137 (59)
Male	28 (39)	28 (41)	12 (44)	28 (42)	96 (41)
Race, n (%)					
White	53 (75)	58 (85)	27 (100)	54 (81)	192 (82)
Other (Non-White)	18 (25)	10 (15)	0	13 (19)	41 (18)
Weight, kg					
Mean (SD)	69.2 (22.5)	70.2 (15.7)	72.7 (19.9)	73.2 (18.4)	71.0 (19.2)
Min-Max	31.5 - 165.0	35.0 - 108.9	45.6 - 111.0	43.6 - 128.7	31.5 - 165.0
Tobacco Use, n	13	14	15	13	55
User, n (%)	4 (6)	2 (3)	2 (7)	3 (4)	11 (5)
Non-user, n (%)	9 (13)	12 (18)	13 (48)	10 (15)	44 (19)
Duration of pain condition (yr)					
Mean (SD)	2.0 (2.4)	2.0 (2.7)	2.0 (1.9)	2.2 (2.4)	2.0 (2.4)
Lifetime chronic opioid use-all conditions (yr)					
Mean (SD)	1.8 (2.5)	1.8 (2.2)	2.1 (3.5)	2.0 (2.4)	1.9 (2.5)
Duration of current opioid therapy (yr)					
Mean (SD)	0.8 (0.9)	0.7 (1.4)	0.9 (1.4)	1.1 (1.6)	0.8 (1.4)

Efficacy: The mean number of SCBMs over the 3-week treatment period was higher in the alvimopan groups compared with the placebo group. The mean change from baseline was also higher in the alvimopan groups compared with the placebo group. However, these differences did not achieve statistical significance.

Primary Efficacy Endpoint: SCBM Frequency (ITT Population)

SCBM Frequency	Placebo N=71	Alvimopan 0.5mg BID N=68	Alvimopan 1mg QD N=27	Alvimopan 1mg BID N=67
Baseline, n	66	67	25	63
Mean (SD)	0.88 (1.20)	0.91 (0.97)	0.74 (0.81)	0.78 (0.98)
3-Week Treatment Period, n	67	67	25	63
Mean (SD)	2.42 (2.71)	2.81 (3.00)	2.50 (3.32)	2.92 (2.79)
Mean change[1] (SE)	1.55 (0.35)	1.90 (0.37)	1.76 (0.62)	2.14 (0.34)
95% CI	(0.86, 2.25)	(1.15, 2.64)	(0.48, 3.03)	(1.46, 2.82)
Tmt diff vs. Placebo	---	0.34	0.20	0.59
95% CI	---	(-0.67,1.35)	(-1.15,1.56)	(-0.38,1.55)
p-value[2]	---	0.529	---	0.515

1. Mean change from baseline.
2. Wilcoxon rank sum test vs. placebo. P-values for the 0.5mg BID and 1mg BID dose groups were adjusted for multiple comparisons using Hommel's general multiple Simes procedure. Treatment arm Alvimopan 1mg QD was discontinued by Amendment 5, therefore there is no adjusted multiple comparison P-value for this arm.

Similar changes were observed for BMs, SBMs, and CBMs. Both alvimopan BID regimens statistically significantly increased SBM frequency compared with placebo over the 3-week treatment period.

SBM Frequency (ITT Population)

SBM Frequency	Placebo N=71	Alvimopan 0.5mg BID N=68	Alvimopan 1mg QD N=27	Alvimopan 1mg BID N=67
Baseline, n	66	67	25	63
Mean (SD)	2.61 (2.55)	2.28 (2.73)	2.00 (1.77)	2.41 (2.64)
3-Week Treatment Period, n	67	67	25	63
Mean (SD)	4.23 (3.67)	5.10 (4.45)	4.70 (5.53)	5.50 (3.94)
Mean change (SE)	1.60 (0.49)	2.82 (0.49)	2.70 (1.01)	3.08 (0.49)
Tmt diff vs. Placebo	---	1.22	1.10	1.48
95% CI	---	(-0.15, 2.59)	(-0.91, 3.12)	(0.11, 2.86)
p-value[1]	---	0.039	---	0.039

1. Wilcoxon rank sum test vs. placebo. P-values for the 0.5mg BID and 1mg BID dose groups were adjusted for multiple comparisons using Hommel's general multiple Simes procedure. Treatment arm Alvimopan 1mg QD was discontinued by final protocol, therefore there is no adjusted multiple comparison P-value for this arm.

The average OBD Global Improvement responder rates, reflecting the proportion of weeks a subject was an OBD Global Improvement responder, were slightly higher in the alvimopan 1mg BID and 0.5mg BID treatment groups compared with placebo over the 3-week treatment period; however, these differences were not statistically significant.

Over the 3-week treatment period, there were slight decreases in stool consistency and straining scores and percentage of BMs with incomplete evacuation for all treatment groups. There were no statistically significant differences between the alvimopan

treatment groups and placebo for the 3-week treatment period average BM symptom ratings.

The PAC-SYM overall and subscale scores were similar for the alvimopan 0.5mg BID and 1mg BID groups and placebo at baseline and reflected mild symptom intensity. Baseline scores in the alvimopan 1mg QD group were slightly higher, but due to discontinuation of this treatment arm, the sample size was smaller. Overall and subscale scores decreased slightly for all treatment groups during the 3-week treatment period.

Safety: The majority of subjects were exposed to investigational product for between 11 and 25 days. There were no statistically significant differences between any dose of alvimopan and placebo in the overall incidence of AEs. GI-related AEs occurred most often (27% placebo group, 38% alvimopan 0.5mg BID group, 26% alvimopan 1mg QD group, and 34% alvimopan 1mg BID group).

Most Common Adverse Events (Safety Population)

	Number (%) of Subjects			
Preferred Term	Placebo N=70	Alvimopan 0.5mg BID N=68	Alvimopan 1mg QD N=27	Alvimopan 1mg BID N=65
Any AE	35 (50)	39 (57)	18 (67)	39 (60)
Any GI-related AE	19 (27)	26 (38)	7 (26)	22 (34)
Diarrhea	6 (9)	11 (16)	2 (7)	8 (12)
Vomiting	6 (9)	5 (7)	1 (4)	5 (8)
Nausea	7 (10)	5 (7)	1 (4)	4 (6)
Abdominal pain	2 (3)	10 (15)	3 (11)	6 (9)
Dyspepsia	1 (1)	1 (1)	0	3 (5)
Any General Disorders and Administration Site Conditions AEs	11 (16)	9 (13)	1 (4)	11 (17)
Pyrexia	1 (1)	1 (1)	0	5 (8)
Pain	4 (6)	2 (3)	0	3 (5)
Edema, peripheral	1 (1)	2 (3)	1 (4)	3 (5)
Any Infections and Infestations AEs	5 (7)	5 (7)	5 (19)	11 (17)
Sinusitis	0	1 (1)	2 (7)	2 (3)
Any Nervous System Disorders AEs	4 (6)	5 (7)	2 (7)	7 (11)
Headache	2 (3)	2 (3)	0	3 (5)
Any Drug-related AE	13 (19)	13 (19)	5 (19)	17 (26)
Any Drug-related GI AE	12 (17)	13 (19)	5 (19)	13 (20)
Diarrhea	3 (4)	7 (10)	2 (7)	6 (9)
Abdominal pain	2 (3)	7 (10)	3 (11)	6 (9)
Nausea	3 (4)	1 (1)	0	3 (5)
Vomiting	2 (3)	0	0	4 (6)

Ten subjects died during the study: one subject receiving placebo, three subjects receiving alvimopan 0.5mg BID, two subjects receiving alvimopan 1mg QD, and four subjects receiving alvimopan 1mg BID. None of the deaths were considered by the investigator to be related to the investigational product, but possibly due to underlying disease/progression of cancer. Overall, 12% of subjects experienced SAEs, ranging from 10% in the placebo group to 19% in the alvimopan 1mg QD group. Pain was the most frequently reported SAE for 4 subjects (3 in the placebo group). Abdominal pain, diarrhea, and vomiting were reported in two subjects each. All other SAEs were reported by one subject each in any treatment group.

The frequency of withdrawal for all other AEs was low and similar across all treatment groups. Twelve percent of subjects withdrew from the study due to AEs. Withdrawal rates were higher in the alvimopan 1mg QD (22%) and alvimopan 1mg BID (14%) groups compared with the alvimopan 0.5mg BID and placebo groups (9% each). Diarrhea and abdominal pain were the AEs most commonly leading to withdrawal, the majority of which occurred during treatment with alvimopan 1mg BID.

Baseline pain intensity scores were comparable for the treatment groups and remained relatively constant during the 3-week treatment period as well as the 2-week follow-up period. The total score and all symptom scores of the modified Himmelsbach score remained essentially unchanged during the treatment and follow-up phases of the study.

Clinically important effects on laboratory analytes for hematologic, hepatic, or renal function were not observed.

Pharmacokinetics: There was no accumulation of alvimopan or metabolite throughout the study in the small subset of subjects who had pharmacokinetic assessments.

Pharmacogenetics: No pharmacogenetic analyses were conducted for this study.

Health Outcomes: Information on quality of life is limited as data collection was discontinued with Amendment 4. Nonetheless, subjects with cancer-related pain and OBD appear to have quality of life scores similar to those of a non-cancer population but worse relative to other chronic medical conditions across all eight domains of the SF-36, a generic quality of life instrument. Results from the PAC-QOL, a constipation-specific quality of life instrument, failed to show a treatment effect.

Conclusions: SB-767905/008 showed that competitive antagonism of opioid analgesics at the μ-opioid receptor by alvimopan is well tolerated and associated with a significant increase in the frequency of spontaneous bowel movements and without compromising analgesia. The study design did not allow clear separation from placebo for many endpoints, however. The severity of OBD during screening was less than that seen in non-cancer populations, possibly due to the liberal standardized bowel regimen. These findings also suggested that the alvimopan 0.5mg BID regimen provided the best benefit-to-risk profile.

- More prevalent per protocol laxative use and allowing stool softeners resulted in more frequent CBMs and BMs at baseline than in other studies. SCBMs and SBMs

at baseline were also more frequent vs. other studies, despite less opportunity for spontaneous events. This may have been driven in part by stool softener use.

- Reduced opportunity for improvement, coupled with the strong placebo response produced by the per-protocol bowel regimen, resulted in non-significant improvements in most endpoints vs. placebo during treatment, including the primary endpoint.
- Subjects experienced a statistically significant improvement in SBM frequency during the 3 week study period, suggesting that there is a clinical benefit in this population despite the confounds present in the design.
- No incremental benefit was observed with the alvimopan 1mg BID regimens on BM frequency or symptom relief compared with the alvimopan 0.5mg BID regimen.
- A higher incidence of withdrawals due to GI AEs was observed in the alvimopan 1mg QD and 1mg BID regimens compared with the alvimopan 0.5mg BID regimen.
- Although AEs affecting the GI tract were expected based upon alvimopan's mechanism of action, withdrawal rates for AEs were relatively low, indicating that alvimopan treatment was generally well-tolerated at the doses used in this study.
- There was no evidence that alvimopan antagonized opioid analgesia or precipitated systemic opioid withdrawal symptoms.

Date of Report: February 2007