

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-775

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-775	Submission Date(s): 9/15/06, 1/18/07, 3/5/08
Brand Name	Entereg
Generic Name	Alvimopan
Reviewer	Sue-Chih Lee, Ph.D.
Deputy Director	Hae-Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Gastroenterology Products
Sponsor	Adolor
Submission Type; Code	Resubmission
Formulation; Strength(s)	Capsules, 12 mg
Proposed Dosing regimen	<ul style="list-style-type: none">• 12 mg at 30 min to 5 hrs prior to surgery• 12 mg BID beginning the day after surgery for a maximum of 7 days while the patient is hospitalized
Indication	Treatment of postoperative ileus

1. EXECUTIVE SUMMARY

1.1 Recommendation

From a clinical pharmacology standpoint, the bioequivalence study has demonstrated that one 12-mg capsule is bioequivalent to two 6-mg capsules. This conclusion was made after taking into consideration the DSI inspection results. Thus, the 12 mg capsules may be approved provided that the Division of Gastroenterology Products finds the NDA acceptable for approval. The comment below regarding the bioanalytical method validation should be communicated to the sponsor.

1.2 Comments (to-be-conveyed to the sponsor)

Plasma samples for the BE study was analyzed by [REDACTED]. The DSI Inspection report of May 2, 2008, stated that the assay validation data generated in the alvimopan freeze-/thaw [REDACTED] stability study, long term frozen [REDACTED] stability study, and [REDACTED] stability study are not reliable. Although these deficiencies do not impact the acceptability of the BE study, the sponsor should be aware of this issue and take appropriate measures to correct the problems for future submissions.

1.3 Phase IV Commitments

N/A

1.4 Summary of Clinical Pharmacology Findings

Background

Alvimopan (ADL 8-2698) is a novel μ -opioid receptor antagonist proposed for the treatment of postoperative ileus. The inhibitory effects of opioids on gastrointestinal (GI) motility are thought to be primarily mediated through μ -opioid receptors located within the enteric nervous system. Alvimopan is intended to act peripherally without producing reversal of the desired, centrally mediated, analgesic effects of opioids.

This is the third review cycle for the NDA. In the original NDA application submitted on 6/25/04, the sponsor was seeking [REDACTED]. An Approvable letter was issued by the Agency on June 21, 2005, due to inadequate efficacy data. In the sponsor's complete response dated May 9, 2006, the sponsor indicated in the CMC section that they intended to seek approval of the 12 mg capsules. The sponsor also stated in the CMC section that they had conducted a BE study (Protocol 14CL130) comparing the two different strengths of capsules and the BE study report had been submitted to the IND. Upon receiving the above information in September 2006 from the reviewing chemist, we requested that the sponsor submit the BE study report to this NDA. The sponsor responded on September 15, 2006. Subsequently, it was determined that there was insufficient time to conduct a thorough review of the study by the Office of Clinical Pharmacology and the Division of Scientific Investigations before the action date. A cursory review of the BE study was conducted and an information request was made, which included a request for the electronic dataset. The Agency issued an approvable letter on 11/3/06 because of safety concerns and required that the sponsor submit the 12-month safety findings and develop a risk management plan. The sponsor responded to the clinical pharmacology information request on January 18, 2007, and submitted on 8/9/07 a complete response to the Agency's approvable letter of 11/3/06. The BE study is thus the subject of this review. Due to late receipt of additional clinical dataset and statistical analyses which constituted a major amendment to the NDA, the PDUFA due date for this application was extended for 3 months to May 10, 2008.

Review of the bioequivalence study (Protocol 14CL130)

Formulation:

The formulation of the 12 mg capsules is similar to that of the 6 mg capsules. The capsule formulations are simply alvimopan dispersed in PEG [REDACTED] to a final fill weight of 300 mg. Because PEG [REDACTED] might alter the absorption of alvimopan, the BE study was reviewed.

BE Study Design:

This was an open-label, randomized, single dose, two-sequence crossover study. Eighty-eight healthy male subjects (age: 24.8 ± 7.3 yrs; wt: 77.1 ± 9.1 kg) were enrolled and

randomly assigned to one of two treatment sequences. Subjects received under fasting conditions single 12 mg dose (two 6 mg capsules or one 12 mg capsule) of alvimopan in each of the two study periods. There was a 7- to 14-day washout between the two treatment periods. Plasma samples were collected for up to 36 hours postdose.

PK parameters for alvimopan only were included in the BE analysis. The PK parameters for ADL 08-0011, the active compound generated through metabolism by the gut flora, could not be accurately estimated due to inadequate sampling scheme for ADL 08-0011. This is not considered an issue according to the SUPAC guidance.

Results:

PK Parameters: The arithmetic mean PK parameters of alvimopan are provided in Table 1. High intersubject variability (CV: 50-60%) in these parameters was observed, which is expected based on previous study findings.

Table 1. Arithmetic mean (%CV) alvimopan PK parameters following single 12-mg dose of Entereg administered as one 12-mg capsule or two 6-mg capsules in 87 healthy male subjects

Treatment	AUC _{0-inf} ng.hr/mL	AUC _t ng.hr/mL	C _{max} ng/mL	T _{max} hr
1 x 12 mg (Test)	43.4* (51.3%)	39.0 (57.8%)	9.9 (59.9%)	2.2 (1.0-4.0)
2 x 6 mg (Reference)	40.6** (54.6%)	37.4 (58.7%)	9.7 (63.3%)	2.0 (0.8-6.0)

*N=82; **N=83

BE analysis: Table 2 presents the 90% confidence intervals using two one-sided tests for the geometric mean ratios (Test/Reference) of both C_{max} and AUC as provided by the sponsor. Since the 90% CI for both C_{max} and AUC were within the 80-125% range, the sponsor concluded that one 12-mg capsule was bioequivalent to two 6-mg capsules.

Table 2: Sponsor's analysis results – Geometric Means for Test and Reference Groups, Test/Reference Ratio and 90% CI

Parameter	N	Test Group (T)	Reference Group (R)	Ratio (T/R)	90% CI for Ratio
AUC _{0-inf} (ng.hr/mL)	78*	37.6	33.3	113.2	104.8-122.1
AUC _t (ng.hr/mL)	87	30.8	29.9	102.8	93.9-112.6
C _{max} (ng/mL)	87	7.7	7.5	102.8	93.4-113.1

*When the extrapolated portion of the AUC was >20% of the overall AUC, the value was excluded from the analysis.

DSI inspection findings:

Both the clinical site and analytical site for the BE study (Protocol 14CL130) were inspected. The clinical site was found acceptable. However, Form FDA 483 was issued regarding the analytical site. The deficiencies are listed in the DSI inspection report dated May 2, 2008 (see Appendix 1).

Evaluation on DSI findings:

The deficiencies cited in Form 483 were evaluated. For deficiencies that could result in biased outcome, the affected subjects were excluded from the dataset and reanalysis was performed by this reviewer using WINNONLIN. The reanalysis results showed that the 90% CI for C_{max} and AUC_t were within the 80-125% range but the 90% CI for AUC_{0-inf} was 96.0-128.1% (Table 3). Nevertheless, we do not consider the findings for AUC_{0-inf} will result in clinically significant difference between the two capsule strengths.

**Table 3: This reviewer's analysis results –
Test/Reference Ratio and 90% CI (excluding Subjects #55-57 and #82-86)**

Parameter	N	Ratio (T/R)	90% CI for Ratio
AUC _{0-inf} (ng.hr/mL)	70	110.9	96.0-128.1
AUC _t (ng.hr/mL)	79	102.2	84.7-123.3
C _{max} (ng/mL)	79	102.0	84.1-123.8

Conclusion:

Based on the above reanalysis results, it is concluded that one 12-mg Entereg capsule was bioequivalent to two 6-mg Entereg capsules.

Individual Study review

Protocol 14CL130:

A Phase 1, Open-Label, Single-Dose, Two-Sequence Crossover Study to Determine the Bioequivalence of One Alvimopan 12 mg Capsule Relative to Two Alvimopan 6 mg Capsules in Healthy Male Subjects

Objective:

The objective of this study was to assess the bioequivalence of one alvimopan 12 mg capsule relative to two 6 mg capsules as measured by PK Parameters of alvimopan in healthy male subjects.

Formulation:

The formulation of the 12 mg capsules is similar to that of the 6 mg capsules. The capsule formulations are simply alvimopan dispersed in PEG. The comparative components and composition information is listed in Table 4.

Table 4: Components and composition of Entereg Capsules

Components	Composition (mg/Tablet)	
	6-mg Capsules	12-mg Capsules
Alvimopan	6.0 ¹	12.0 ¹
PEG		
Total Weight		300.0

¹Quantity on the anhydrous basis, i.e., the actual weight takes into account

Study Design:

This study was an open-label, randomized, single dose, two-sequence crossover study.

Eighty-eight healthy male subjects (age: 24.8 ± 7.3 yrs; wt: 77.1 ± 9.1 kg) were enrolled and randomly assigned to one of two treatment sequences. Subjects received under fasting conditions single 12 mg doses of alvimopan with a 7- to 14-day washout separating the two treatment periods. During each dosing period subjects were to: (1) fast for at least 10 hours before and 4 hours after receiving alvimopan (while fasting, subjects were allowed to drink water ad lib except for 1 hour before and 1 hour after each dose); (2) drink 240 mL of water 30 minutes before each alvimopan dose (3) take each dose with 240 mL of water; and (4) have a 2200 calorie/day diet in accordance with the American Heart Association diet at least 4 hours after administration of each dose.

Treatments: (1) one 12-mg alvimopan capsule (Test)
(2) two 6-mg alvimopan capsules (Reference)

Sample size: The sample size calculation was based on the estimates of within subject variability obtained from the data for $AUC_{0-\infty}$ and C_{max} in a previous study (14CL1193). Estimates of the within-subject variability were 39.0% and 46.5% for log-transformed $AUC_{0-\infty}$ and log-transformed C_{max} . Based on these estimates of variability it was estimated that 88 subjects would be needed to provide at least 90% power to demonstrate equivalence for both $AUC_{0-\infty}$ and C_{max} .

Sixteen serial whole blood samples were collected to determine alvimopan plasma concentrations before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, and 36 hours after each dose.

Blood samples for the determination of alvimopan were analyzed by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method at ~~██████████~~

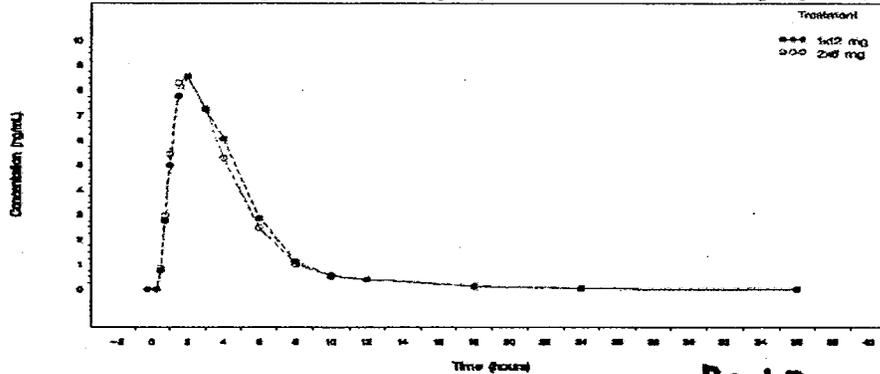
Pharmacokinetic parameters of alvimopan were estimated by GlaxoSmithKline Clinical Pharmacokinetics Modeling and Simulation, Research Triangle Park using the noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition Version 4.1 (Pharsight Corporation, Mountain View, CA). Actual elapsed times were used to estimate all plasma pharmacokinetic parameters for alvimopan.

Results

Mean alvimopan plasma concentration-time profiles for the Test (one 12 mg capsule) and the Reference (two 6 mg capsules) groups were generally similar (Figure 1). Plasma alvimopan concentration peaked at approximately 2 hours postdose. The arithmetic mean

(±SD) PK parameters for the evaluable patients for both Test and Reference groups are presented in Table 5.

Fig. 1: Mean Plasma Alvimopan Concentration-Time Profiles following single oral administration of alvimopan 12 mg (Test: 1 x 12 mg capsules; Reference: 2 x 6 mg capsules)



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Table 5: Arithmetic Mean PK Parameters for Test and Reference Treatments

Treatment	AUC _{0-inf} ng.hr/mL	AUC _t ng.hr/mL	C _{max} ng/mL	T _{max} hr
1 x 12 mg (Test)	43.4 (51.3%)	39.0 (57.8%)	9.9 (59.9%)	2.2 (1.0-4.0)
2 x 6 mg (Reference)	40.6 (54.6%)	37.4 (58.7%)	9.7 (63.3%)	2.0 (0.8-6.0)

Analysis of log-transformed data using ANOVA models that included period, treatment, sequence, and subject(sequence) revealed a statistically significant period effect for AUC_{0-∞} and C_{max} (Table 6). The AUC_{0-∞} and C_{max} were lower for subjects receiving 2 x 6 mg doses in Period 2. There was no sequence or treatment effect. Since the period effect was included in the final model, this factor was taken into account in the final results.

Table 6: Geometric Means of AUC_{0-inf} and C_{max} Values for Test and Reference Groups by Period

	n	Test Group (1 x 12 mg capsule)	n	Reference Group (2 x 6 mg capsules)
Period 1				
AUC _{0-∞} (hr-ng/mL) ^a (90% CI)	42	37.9 (32.6 – 44.0)	44	40.3 (35.3 – 46.0)
C _{max} (ng/mL) ^a (90% CI)	43	8.54 (7.0 – 10.4)	44	9.58 (8.3 – 11.1)
Period 2				
AUC _{0-∞} (hr-ng/mL) ^a (90% CI)	40	36.8 (31.2 – 43.5)	39	28.2 (23.3 – 34.1)
C _{max} (ng/mL) ^a (90% CI)	44	7.01 (5.6 – 8.8)	43	5.92 (4.7 – 7.5)

The sponsor's analysis on the geometric means, Test/Reference ratio and the 90% confidence intervals are provided in Table 7. The 90% confidence intervals for Cmax and AUC fell within the 80-125% range. Therefore, the sponsor concluded that one 12-mg capsule was bioequivalent to two 6-mg capsules.

Table 7: Geometric Means for Test and Reference Groups, Test/Reference Ratio and 90% CI

Parameter	N	Test Group (T)	Reference Group (R)	Ratio (T/R)	90% CI for Ratio
AUC _{0-inf} (ng.hr/mL)	78*	37.6	33.3	113.2	104.8-122.1
AUCt (ng.hr/mL)	87	30.8	29.9	102.8	93.9-112.6
Cmax (ng/mL)	87	7.7	7.5	102.8	93.4-113.1

This reviewer's analysis results were somewhat different. The 90% CI for both Cmax and AUCt ratios were within the 80-125% range but the 90% CI for AUC0-inf was 97.6-127.3%. Nevertheless, we do not consider the findings for AUC0-inf will result in clinically significant difference between the two capsule strengths.

Comments:

- Subjects were required to take 240 mL of water 30 minutes before dosing and another 240 mL of water with each dose. This is a deviation from the conventional design for BE studies, in which subjects take 240 mL of water at the time of dosing without the additional 240 mL of water 30 minutes before dosing. Upon internal discussion within DCP3, this was considered not to affect the final outcome.

Bioanalytical method

The analytical method for assay of plasma alvimopan is acceptable for the BE study based on the data provided in the NDA. It was noted that the reasons for sample re-assay were not totally clear.

Plasma samples for the BE study was analyzed by [REDACTED]. The assay method and assay performance according to the information submitted to the NDA are summarized below.

Method: The assay method used a [REDACTED] process to extract alvimopan and the internal standard [REDACTED] from plasma. The solvent was evaporated, and the residue was dissolved in mobile phase, a portion of which was injected into a liquid chromatographic system. Detection was by MS/MS by the use of a [REDACTED] mass spectrometer. Calibration curves and quality control samples were part of each run.

Assay performance: The validation results were provided in the original NDA and were acceptable based on the data provided. The ranges of the assay for alvimopan (ADL 8-2698) was from 0.25 ng/mL to 250 ng/mL. The limit of quantification was 0.25 ng/mL for alvimopan. Quality control standards for the BE study samples at 3 concentrations (low: 0.75 ng/mL; middle: 25 ng/mL; and high: 175 ng/mL) were included in each analytical run. The inter-assay precision, expressed as CV% was less than 10.0% for alvimopan; and the inter-assay accuracy, expressed as a % deviation of the mean from the

theoretical (%DMT), was within $\pm 10.0\%$ for alvimopan. Stability of ADL 8-2698 in plasma QC samples (with sodium heparin as anticoagulant) after frozen storage for an interval of [REDACTED] has been established. Stability of ADL 8-2698 in stock solution has been established for 229 and 238 days, respectively, which is a storage interval [REDACTED] than that for the solutions used in the preparation of the calibration and QC samples for this study.

Impact of DSI findings on the BE study

The inspections of Alvimopan Study 14CL130 were completed. No Form FDA-483 was issued for the clinical site but Form FDA-483 was issued for the analytical site, [REDACTED] (See Appendix 1.) Following careful consideration of the 483 items, it was determined that the deficiencies will not affect the conclusion of the BE study. The deficiencies are addressed as follows:

#1: Out of the 3 QC samples (0.25, 25 & 250 ng/mL) used, the highest concentration (250 ng/mL) was not useful because the highest C_{max} value observed in the study was 26 ng/mL. It would have been more appropriate to add one QC sample concentration between 0.25 and 25 ng/mL. However, in view of the comparative nature of a BE study, it is unlikely that this deficiency will significantly impact the results.

The failed QC samples in batch 48, however, rendered Period 1 data from Subjects 82-86 unreliable. As such, these subjects were excluded from this reviewer's analysis (see Table 8).

#2, and #3: Deficiencies related to validation sample handling are considered unlikely to change the BE study conclusion because of the comparative nature of the study, i.e., any change in the assay results for the test product would also be observed with the reference product.

#4: ADL 08-0011: This compound was not included in the BE testing and, therefore, the issues related to assay of this compound is not of concern.

#5: Matrix effect was noted in the first seven analytical runs of the study. This event was not reported in the bioanalytical report. However, since the problems were corrected and reassay of these seven runs was performed, the event would not have consequences on the BE study outcome.

#6 & 7: Several plasma samples were reassayed to confirm unexpected results or for other reasons. There were no objective criteria established a priori. However, the reassay results were mostly similar to the original results. Only 5 samples from 3 subjects (Subjects #55-57) showed significant differences in the results. As such, these three subjects were also excluded in this reviewer's analysis (Table 8).

Reviewer's BE analysis

As stated above, some deficiencies cited in the Form 483 could potentially result in biased outcome. Therefore, BE analysis was conducted using a dataset that excluded the eight subjects affected by the Form 483 findings. The analysis results showed that the 90% CI for Cmax and AUCt were within the 80-125% range but the 90% CI for AUC_{0-inf} was 96.0-128.1% (Table 8). Nevertheless, we do not consider the findings for AUC_{0-inf} will result in clinically significant difference between the two capsule strengths, i.e., one 12-mg Entereg Capsule is bioequivalent to two 6-mg Entereg capsules.

**Table 8: Reviewer's analysis results –
Test/Reference Ratio and 90% CI (excluding Subjects #55-57 and #82-86)**

Parameter	N	Ratio (T/R)	90% CI for Ratio
AUC _{0-inf} (ng.hr/mL)	70	110.9	96.0-128.1
AUCt (ng.hr/mL)	79	102.2	84.7-123.3
Cmax (ng/mL)	79	102.0	84.1-123.8

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Attachment 1: DSI Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 2, 2008

TO: Donna Grietel, MD
Director
Division of Gastroenterology Products, (HFD-180)

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *CTV 515108*
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-775, Entereg®
(Alvimopan) 6 mg, 12 mg Capsules, Sponsored by
Adolor Corporation.

At the request of the Division of Gastroenterology Products (DGP), the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Study 14CL130: Phase I, Open-label, Single-dose, Two-Sequence Crossover Study to Determine the Bioequivalence of one Alvimopan 12 mg Capsules Relative to two Alvimopan 6 mg Capsules in Healthy Male Subjects.

The clinical and analytical portions of the study were conducted at _____

_____ respectively. No Form FDA 483 was issued following the inspection of the clinical portion of the study (4/4-10/08). Following the inspection of the analytical portion (4/22-25/08) Form FDA 483 was issued (Attachment 1). Our evaluation of the significant findings is as follows:

1. The quality control samples (QCs) and calibration range (0.25 to 250 ng/ml) for alvimopan and ADL 08-0011 used in the analytical runs were not representative of the alvimopan and ADL 08-0011 plasma concentrations observed in study plasma samples. For example, the mean peak alvimopan concentration (C_{max}) following dosing of one 12 mg (test group) and two 6 mg (reference group) alvimopan capsules were both < 8 ng/ml, but the low, mid, and high alvimopan QCs used were 0.75, 25, and 175 ng/ml, respectively.

Almost all individual subject plasma samples obtained in the study had alvimopan and ADL 08-0011 (active metabolite of alvimopan) concentrations below the mid QC (25 ng/ml). Thus, the high QC (175 ng/ml) of alvimopan and ADL-08-0011 were not representative of the concentrations found in the subject plasma samples.

A review of the alvimopan QCs results (Attachment 2) however, showed that most ($\geq 75\%$) of the low and mid alvimopan QCs results in the accepted runs met the acceptance criteria (i.e. <15% error), with the exception of batch 48, where only 50% of QCs in the low and mid levels passed. As the high QC is not representative of subject plasma concentration and only 50% of the low and mid alvimopan QC passed in batch 48, the alvimopan data (i.e., all period 1 data from subjects 82, 83, 84, 85, and 86) generated in this batch is not reliable.

Regarding the results of the ADL 08-0011 QCs, we found that there were more failed low and mid QCs than in alvimopan (Attachment 3). In addition, the ADL 08-0011 standard curves generated in the study had a high failure rate (31%; 20 of 64 curves failed). Moreover, the sensitivity of the LC/MS/MS assay for the analysis of ADL -0-0011 is also questionable (see discussion under 483 Item 4 below).

2. Failure to use freshly prepared calibration curves in the long term frozen and freeze/thaw (F/T) cycles stability studies for alvimopan and ADL 08-0011. For example: calibration standards for alvimopan and ADL 08-0011 were prepared and then frozen on February 27, 2003. These calibration standards were then used in a

validation run to evaluate the cycles F/T stability for alvimopan and ADL 08-0011 on April 16, 2003. The calibration standards used in the long term frozen stability validation run on September 19, 2002 was prepared three days before the run on September 16, 2002.

3. The (i.e., process sample) stability data for alvimopan and ADL 08-0011 provided in the validation report were not meaningful in that both calibration standards and process stability samples were stored under the same condition (i.e., at room temperature for), prior to injection into the LC/MS/MS system.

Due to the inspectional findings in 483 Items 2 and 3, the data generated in the freeze/thaw stability study, long term frozen stability study and stability studies are questionable.

4. The assay sensitivity for ADL 08-0011 is questionable in that the ADL 08-0011 concentrations in a large number (>50%) of total subject plasma samples were below the limit of quantitation (LOQ).

Due to the inadequate assay sensitivity, the elimination half-life of many study subjects could not be accurately determined. This observation along with the findings in 483 Item 1 (see comments under 483 Item above) raise questions of whether the assay can be used to determine ADL-8-0011 concentrations from plasma samples obtained in the study. However, following the inspection, DSI was informed by OCP that data from ADL 08-011 was not used to establish bioequivalence between the test and reference products.

5. Matrix effect study was not conducted during validation of the LC/MS/MS method. A matrix effect was noted in the first analytical runs of study subject plasma samples requiring cleaning of the LC/MS/MS system and re-assaying of all samples in these seven runs. This event was not discussed in the bioanalytical report.

Based on source records, a significant difference in internal standard responses was observed between study subject samples and the pooled calibrators and QC samples

6. Several plasma samples were re-assayed to confirm results due to unexpected alvimopan or ADL 08-0011 plasma concentrations (i.e., pharmacokinetic re-assays). There were no objective criteria established a priori for these re-assays.
7. Several plasma samples were re-assayed due to internal standard variation. There were no objective criteria established for these re-assays.

In most of the samples subjected to re-assay due to PK or internal standard (IS) variations, the alvimopan concentrations in the original assay are only slightly different from the re-assay concentrations. The sample that showed more substantial differences are listed in the table below.

Subject #	Post Dose Time Point	Original vs Reported Concentration (ng/ml)	Comment
55	Period 1, 2h	/	
55	Period 1, 4h		
56	Period 1, 3h		Cmax sample
56	Period 1, 4h		
57	Period 1, 10h		

Since only a few of the reported values are substantially different from the original assayed values, findings in 483 Items 6 and 7 are not likely to have significant impact on the study outcomes. However, this should be confirmed by the OCP reviewer.

During the inspection, the site agreed to implement correction to the above two observations

Conclusion:

Following our evaluation of the inspectional findings, DSI concludes the following:

1. The alvimopan data (i.e., all period 1 data from subjects 82, 83, 84, 85, and 86) generated in batch 48 are not reliable. We recommends that these data be excluded from bioequivalence determination (see discussion in 483 Item 1).
2. The data generated in the alvimopan freeze/thaw stability study, long term frozen stability study, and stability study are not reliable (see comments in 483 Items 2 and 3). The Review Division should consider asking the sponsor to repeat these stability studies using freshly prepared standard curves.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau

Martin K. Yau, Ph.D.

Xikui Chen

Xikui Chen, Ph.D.

Final Classification:

VAI - _____
(Analytical Site)

NAI - _____
(Clinical Site)

Page 6 of 6 - NDA 21-775, Entereg® (Alvimopan) 6mg, 12 mg
Capsules

cc:

HFD-45/RF

HFD-48/Yau/Chen/Himaya/CF

DGP/Matthew Scherer (NDA 22-067)

DCP/Sue-Chih Lee

HFR-CE7545/Larry Austin

HFR-CE8585/Scott Laufenberg

Draft: MKY 5/2/08

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Attachment I

1 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Attachment 2

Table 7
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Quality Control Values for Alvimopan in Human Plasma

Batch	Theoretical Concentration (ng/mL)					
	0.750	% DEV	25.0	% DEV	175	% DEV
001-R2						
002-R2						
003-R2	0.684	-8.8	26.6	6.4	142	18.9 FC
	0.729	-2.8	37.4	49.6	FC 153	12.6
004-R						
005-R	0.799	6.5	23.1	-7.6	144	-17.7 FC
	0.816	8.8	24.0	-4.0	171	-2.3
006-R	0.620	-17.3	FC 26.0	4.0	153	-12.6
	0.783	4.4	26.6	6.4	154	-12.0
007-R	0.738	-1.6	26.5	6.0	154	-12.0
	0.756	0.8	27.1	8.4	158	-9.7
008	0.721	-3.9	25.5	2.0	155	-11.4
	0.763	1.7	26.2	4.8	158	-9.7
009	0.719	-4.1	26.2	4.8	161	-8.0
	0.741	-1.2	27.5	10.0	164	-6.3
010	0.727	-3.1	26.8	7.2	156	-10.9
	0.775	3.3	26.8	7.2	161	-8.0
011	0.777	3.6	25.3	1.2	158	-9.7
	0.951	26.8	FC 26.4	5.6	166	-5.1
012	0.661	-11.9	24.6	-1.6	155	-11.4
	0.772	2.9	25.6	2.4	163	-6.9
013	0.701	-6.5	23.6	-5.6	160	-8.6
	0.717	-4.4	25.5	2.0	160	-8.6
014	0.762	1.6	25.2	0.8	165	-5.7
	0.792	5.6	25.6	2.4	166	-5.1
015	0.663	-11.6	23.0	-8.0	137	21.7 FC
	0.726	-3.2	25.0	0.0	172	-1.7
016	0.645	-14.0	22.3	-10.8	145	17.1 FC
	0.738	-1.6	24.2	-3.2	168	-4.0
017	0.776	3.5	23.9	-4.4	142	18.9 FC
	0.811	8.1	24.3	-2.8	163	-6.9
018	0.843	12.4	25.0	0.0	154	-12.0
	0.892	18.9	FC 26.8	7.2	163	-6.9
019-R	0.705	-6.0	26.7	6.8	167	-4.6
	0.807	7.6	27.9	11.6	169	-3.4
020	0.725	-3.3	23.5	-6.0	163	-6.9
	0.846	12.8	26.7	6.8	173	-1.1
021	0.717	-4.4	1M		164	-6.3
	0.734	-2.1	27.0	8.0	165	-5.7
022	0.674	-10.1	26.3	5.2	159	-9.1
	0.684	-8.8	28.0	12.0	173	-1.1
023	0.645	-14.0	25.3	1.2	162	-7.4
	0.727	-3.1	25.9	3.6	165	-5.7
024	0.695	-7.3	24.1	-3.6	149	-14.9
	0.828	10.4	25.6	2.4	155	-11.4

025		0.706	-5.9		24.9	-0.4	153	-12.6
		0.736	-1.9		26.5	6.0	156	-10.9
026		0.682	-9.1		26.3	5.2	159	-9.1
		0.703	-6.3		26.7	6.8	161	-8.0
027		0.694	-7.5		24.8	-0.8	159	-9.1
		0.695	-7.3		25.5	2.0	163	-6.9
028		0.667	-11.1		26.1	4.4	162	-7.4
		0.821	9.5		27.1	8.4	168	-4.0
029		0.627	-16.4	FC	25.1	0.4	160	-8.6
		0.735	-2.0		27.3	9.2	168	-4.0
030	X5							
031		0.756	0.8		26.6	6.4	166	-5.1
		0.850	13.3		26.7	6.8	184	5.1
032	X2							
033	X2							
034-R	X2							
035	X2							
036	X2							
037	X2							
038		0.765	2.0		27.2	8.8	173	-1.1
		0.778	3.7		27.6	10.4	179	2.3
039		0.615	-18.0	FC	26.8	7.2	157	-10.3
		0.776	3.5		27.2	8.8	168	-4.0
040		0.681	-9.2		26.9	7.6	164	-6.3
		0.743	-0.9		26.9	7.6	168	-4.0
041		0.653	-12.9		24.8	-0.8	163	-6.9
		0.747	-0.4		26.0	4.0	167	-4.6
042	X2							
043		0.642	-14.4		26.0	4.0	169	-3.4
		0.717	-4.4		26.2	4.8	174	-0.6
044		0.682	-9.1		27.1	8.4	167	-4.6
		0.725	-3.3		30.4	21.6	178	1.7
045		0.710	-5.3		26.5	6.0	169	-3.4
		0.731	-2.5		26.7	6.8	173	-1.1
046	X2							
047		0.668	-10.9		23.9	-4.4	155	-11.4
		0.781	4.1		27.2	8.8	165	-5.7
048		0.807	7.6		26.4	5.6	174	-0.6
		0.866	15.5	FC	29.1	16.4	179	2.3
049-R		0.713	-4.9		25.8	3.2	174	-0.6
		0.736	-1.9		27.9	11.6	184	5.1
050		0.706	-5.9		27.7	10.8	168	-4.0
		0.833	11.1		27.9	11.6	171	-2.3
051	X2							
052	X2							
053	X2							
054	X2							
055		0.624	-16.8	FC	26.5	6.0	167	-4.6
		0.657	-12.4		26.8	7.2	178	1.7
056		0.672	-10.4		26.5	6.0	157	-10.3
		0.695	-7.3		27.4	9.6	165	-5.7
057	X2							
058	X2							
059	X2							

060	X2						
061-R	X2						
062-R		0.680	-9.3	24.3	-2.8	156	-10.9
		0.741	-1.2	24.6	-1.6	157	-10.3
063	X2						
064	X2						

n	82	81	82
Mean	0.734	26.2	163
SD	0.0655	1.88	9.19
RSD (%)	8.9	7.2	5.6
DMT(%)	-2.1	4.8	-6.9

FC Failed acceptance criteria
 IM Instrument malfunction
 SP Sample processing error
~~X2 Analyzed for ADL 08-0011 only~~
 X5 Batch number not used

Attachment 3

COPY

Table 8
 Altered Copy
 Quality Control Values for ADL 08-0011 in Human Plasma

Batch		Theoretical Concentration (ng/mL)						
		0.750	% DEV	25.0	% DEV	175	% DEV	
001-R2	SP							
002-R2	SP							
003-R2		0.661	-11.9	26.1	4.4	146	-16.6	FC
		0.812	8.3	41.9	67.6	FC 170	-2.9	
004-R		0.704	-6.1	24.3	-2.8	160	-8.6	
		0.865	-15.3	FC 24.3	-2.8	179	2.3	
005-R		0.706	-3.9	22.5	-10.0	119	-32.0	FC
		0.730	-3.7	25.4	1.6	187	6.9	
006-R	FC							
007-R		0.746	-0.5	26.6	6.4	163	-6.9	
		0.753	0.4	27.1	8.4	163	-6.9	
008		0.549	-26.8	FC 25.1	0.4	154	-12.0	
		0.782	4.3	26.8	7.2	162	-7.4	
009		0.618	-17.6	FC 25.0	0.0	149	-14.9	
		0.674	-10.1	25.3	1.2	149	-14.9	
010		0.697	-7.1	25.8	3.2	146	-16.6	FC
		0.844	12.5	26.4	5.6	162	-7.4	
011		0.822	9.6	25.3	1.2	171	-2.3	
		1.07	42.7	FC 29.0	16.0	FC 181	3.4	
012	FC							
013	FC							
014		0.733	-2.3	25.1	0.4	149	-14.9	
		0.829	10.5	26.2	4.8	151	-13.7	
015		0.682	-9.1	21.4	-14.4	105	-40.0	FC
		0.799	6.5	22.5	-10.0	170	-2.9	
016	FC							
017		0.781	4.1	24.4	-2.4	150	-14.3	
		0.852	13.6	25.8	3.2	159	-9.1	
018		0.801	6.8	25.8	3.2	147	-16.0	FC
		0.975	30.0	FC 26.8	7.2	157	-10.3	
019-R		0.775	3.3	27.5	10.0	165	-5.7	
		0.836	11.5	29.5	18.0	FC 175	0.0	
020		0.683	-8.9	25.3	1.2	173	-1.1	
		0.801	6.8	29.1	16.4	FC 194	10.9	
021		0.705	-6.0	1M		144	-17.7	FC
		0.772	2.9	24.5	-2.0	159	-9.1	
022		0.705	-6.0	27.3	9.2	129	-26.3	FC
		0.733	-2.3	28.9	15.6	FC 185	5.7	
023	FC							
024		0.826	10.1	21.6	-13.6	177	1.1	
		0.954	27.2	FC 30.2	20.8	FC 192	9.7	
025	FC							
026	FC							

027	FC								
028		0.777	3.6	24.0	-4.0		165	-5.7	
		0.842	12.3	29.0	16.0	FC	174	-0.6	
029		0.698	-6.9	25.5	2.0		184	5.1	
		0.898	19.7	FC	28.3		209	19.4	FC
030	X5								
031	XI								
032		0.620	-17.3	FC	26.4	5.6	161	-8.0	
		0.656	-12.5		29.1	16.4	FC	168	-4.0
033		0.620	-17.3	FC	24.7	-1.2	168	-4.0	
		0.642	-14.4		25.5	2.0	180	2.9	
034-R		0.657	-12.4		22.6	-9.6	153	-12.6	
		0.839	11.9		26.4	5.6	163	-6.9	
035		0.777	3.6		28.0	12.0	169	-3.4	
		0.838	11.7		28.5	14.0	170	-2.9	
036		0.755	0.7		24.6	-1.6	147	-16.0	FC
		0.762	1.6		28.3	13.2	159	-9.1	
037		0.842	12.3		26.4	5.6	151	-13.7	
		0.844	12.5		28.4	13.6	172	-1.7	
038		0.741	-1.2		26.6	6.4	165	-5.7	
		0.835	11.3		29.1	16.4	FC	168	-4.0
039	FC								
040		0.675	-10.0		27.9	11.6	165	-5.7	
		0.832	10.9		28.1	12.4	174	-0.6	
041		0.669	-10.8		24.1	-3.6	160	-8.6	
		0.818	9.1		24.9	-0.4	170	-2.9	
042		0.725	-3.3		23.1	-7.6	154	-12.0	
		0.743	-0.9		25.9	3.6	177	1.1	
043		0.580	-22.7	FC	27.0	8.0	170	-2.9	
		0.667	-11.1		28.1	12.4	177	1.1	
044	FC								
045		0.588	-21.6	FC	26.7	6.8	177	1.1	
		0.736	-1.9		27.6	10.4	181	3.4	
046		0.603	-19.6	FC	24.1	-3.6	133	-24.0	FC
		0.716	-4.5		25.5	2.0	197	12.6	
047		0.838	11.7		24.9	-0.4	151	-13.7	
		0.848	13.1		26.5	6.0	171	-2.3	
048	FC								
049-R		0.797	6.3		27.4	9.6	161	-8.0	
		0.831	10.8		29.7	18.8	FC	171	-2.3
050	FC								
051		0.671	-10.5		28.1	12.4	168	-4.0	
		0.702	-6.4		28.2	12.8	172	-1.7	
052	FC								
053	FC								
054	FC								
055	FC								
056	FC								
057	FC								
058		0.834	11.2		27.1	8.4	141	-19.4	FC
		0.868	15.7	FC	28.6	14.4	151	-13.7	

059	FC									
060		0.642	-14.4		19.1	-23.6	FC	145	-17.1	FC
		0.650	-13.3		25.8	3.2		158	-9.7	
061-R	FC									
062-R		0.637	-15.1	FC	22.1	-11.6		158	-9.7	
		0.720	-4.0		26.0	4.0		162	-7.4	
063		0.613	-18.3	FC	25.2	0.8		164	-6.3	
		0.649	-13.5		30.0	20.0	FC	169	-3.4	
064		0.665	-11.3		23.8	-4.8		133	-24.0	FC
		0.743	-0.9		24.6	-1.6		164	-6.3	
<hr/>										
n		80			79			80		
Mean		0.750			26.3			163		
SD		0.0963			2.81			16.7		
RSD (%)		12.8			10.7			10.2		
DMT(%)		0.0			5.2			-6.9		

FC Failed acceptance criteria
 IM Instrument malfunction
 SP Sample processing error
 X1 Analyzed for Alvimopan only
 XS Batch number not used

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Xikui Chen
5/5/2008 04:22:03 PM
COMPLIANCE OFFICER

Martin Yau
5/5/2008 04:25:47 PM
CSO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sue Chih Lee
5/8/2008 09:11:37 AM
BIOPHARMACEUTICS

Hae-Young, I have addressed the DSI findings in the
review. Please see if it looks ok. Thanks.

Hae-Young Ahn
5/8/2008 09:29:49 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-775	Submission Date(s): 2/24/06, 5/9/06, 9/15/06
Brand Name	Entereg
Generic Name	Alvimopan
Reviewer	Sue-Chih Lee, Ph.D.
Acting Team Leader	Abi Adebawale, Ph.D.
Pharmacometrics Reviewer/Team Leader	Jogaro Gobburu, Ph.D.
OCPB Division	Division of Clinical Pharmacology III
OND division	Division of Gastroenterology Products
Sponsor	Adolor
Submission Type; Code	Resubmission
Formulation; Strength(s)	Capsules, 12 mg
Proposed Dosing regimen	<ul style="list-style-type: none">• 12 mg at 30 min to 5 hrs prior to surgery• 12 mg BID beginning the day after surgery for a maximum of 7 days while the patient is hospitalized
Indication	Treatment of postoperative ileus

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1. EXECUTIVE SUMMARY

1.1 Recommendation

From the standpoint of the Office of Clinical Pharmacology, the Clinical Pharmacology and Biopharmaceutics section of the NDA is acceptable for the [REDACTED] capsules provided that a satisfactory agreement can be reached between the Agency and the sponsor regarding the label language. The acceptability of the 12-mg capsules has not been fully evaluated because the bioequivalence study supporting the 12-mg capsules was submitted late in the review cycle. The comments below should be communicated to the sponsor.

1.2 Comments

The 12-mg capsule formulation [REDACTED] the BE study to establish the bioequivalence of one 12-mg capsule to two 6-mg capsules was not submitted to the NDA until late in this review cycle (9/15/06). A full evaluation of this BE study could not be conducted in this review cycle because of time constraint. A cursory review of the BE study revealed that the report lacks the following information:

- A. Subjects were required to take 240 mL of water 30 minutes before dosing and another 240 mL of water at the time of dosing. This is a deviation from the conventional design for BE studies, in which 240 mL of water was required only at the time of dosing. The sponsor should explain the purpose and impact of this additional 240 mL water intake 30 minutes before dosing.
- B. The individual PK parameters for the BE study should be submitted as an electronic file in a readily analyzable format.

The sponsor may pursue the approval of the 12-mg strength [REDACTED]

1.3 Phase IV Commitments

N/A

1.4 Summary of Clinical Pharmacology Findings

Background

NDA 21-775 was originally submitted by the Sponsor on June 25, 2004. An Approvable letter was issued by the Agency on June 21, 2005. The clinical pharmacology issues identified following the review of the original NDA are not approval issues but are related to information that may be included in the label. The sponsor submitted a response on February 24, 2006 to address these issues. The complete response, however, was not submitted to the Agency until May 9, 2006 when the clinical issues were addressed.

Mechanism of Action

Alvimopan is a novel μ -opioid receptor antagonist with no agonist activity. The inhibitory effects of opioids on gastrointestinal (GI) motility are considered to be primarily mediated through μ -opioid receptors located within the enteric nervous system. It is intended to act peripherally without producing reversal of the desired, centrally mediated, analgesic effects of opioids.

Following oral administration of Entereg capsules, another compound, designated as ADL 08-0011, was found to be present in the plasma at concentrations higher than those of alvimopan. The sponsor postulated that ADL 08-0011 was produced by gut microflora since *in vitro* metabolism studies failed to detect the presence of this compound. ADL 08-0011 is an antagonist at the μ -receptor and is approximately equipotent to alvimopan in nonclinical and *in vitro* models. In contrast to the relative inability of alvimopan to antagonize the CNS effects of morphine, ADL 08-0011 has been demonstrated to antagonize morphine-induced analgesia. This did not occur, however, until doses were 5-8-fold higher than those to reverse GI effects in the rat with intravenous administration.

Issues identified in the first review cycle:

The clinical pharmacology issues identified were (1) inadequate information on the CYP induction potential of alvimopan and ADL 08-0011, and (2) key questions related to the population PK analysis submitted on May 17, 2005.

Sponsor's response:

In the submission dated February 24, 2006, the sponsor addressed the above issues. In addition, the sponsor submitted a report on an additional concentration-QT response analysis for the thorough QT study.

In this resubmission, the sponsor is pursuing the new 12 mg capsules although this was not apparent to this reviewer until later in the review cycle. Because all the clinical trials were conducted using the 6 mg capsules, information linking the two strengths is necessary. The sponsor provided on September 15, 2006 a BE study report which was originally submitted to IND 56,553 (Serial #229) on August 15, 2005.

Review of the Current Submission

In the current review cycle, the *in vitro* CYP induction study was reviewed by this reviewer. Because the BE study was not submitted to the NDA until late in the review cycle, only a cursory review was conducted to identify additional information needed.

The conclusions are as follows:

- Neither alvimopan nor ADL 08-0011 is a potential inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.
- The following additional information is needed for a full evaluation of the BE study which was designed to demonstrate the bioequivalence of one 12-mg capsule to two 6-mg capsules.

1. Explain the purpose and impact of study design in which subjects were instructed to take 240 mL of water 30 minutes before dosing (and again 240 mL of water at the time of dosing).
2. Provide an electronic file for individual PK parameters in a readily analyzable format.

The QT and population PK analyses were reviewed by Dr. Joga Gobburu, Team leader of Pharmacometrics/OCP. Because the population PK analysis was originally submitted one month before the action date during the first review cycle, a brief review of the analysis was conducted by this reviewer at the time to identify major issues to facilitate a detailed review later on and a full review of the analysis is warranted during this review cycle. This point was emphasized to Dr. Gobburu. The following conclusions are made based on Dr. Gobburu's review of these studies (see Appendix 1):

- There is no evidence of a QT prolongation risk even at the dose of 24 mg BID.
- The sponsor's population PK analysis is acceptable.

Conclusion

The sponsor has satisfactorily addressed the issues raised during the first review cycle and the population PK analysis has been fully evaluated and deemed acceptable. Therefore, the capsules are acceptable from the clinical pharmacology standpoint. The 12-mg capsule formulation the BE study to establish the bioequivalence of one 12-mg capsule to two 6-mg capsules was not submitted to the NDA until late in this review cycle (9/15/06). A full evaluation of the BE study could not be conducted in this review cycle because of time constraint.

**Appears This Way
On Original**

2. Review of Sponsor's Response

Induction potential of alvimopan and ADL 08-0011

Agency's Comment:

The potential of alvimopan and ADL 08-0011 as CYP inducers should be evaluated with hepatocytes from at least 3 donors. (The studies conducted for alvimopan were inadequate and no studies were conducted for ADL 08-0011).

Adolor's Response:

A CYP induction study was conducted as detailed below:

Experimental Design:

The potential of alvimopan and ADL 08-0011 to induce CYP450 was determined in primary cultures of cryopreserved human hepatocytes. Three lots of cryopreserved hepatocytes from 3 human donors were treated once daily for 3 consecutive days with 0.1% dimethylsulfoxide (vehicle), 1 of 3 concentrations of alvimopan (0.5, 5 or 50 μM), 1 of 3 concentrations of ADL 08-0011 (0.5, 5 or 50 μM), or 1 of 3 known human cytochrome P450 enzyme inducers, omeprazole (100 μM), phenobarbital (750 μM) or rifampin (10 μM). After treatment, the rates of phenacetin O-deethylation (CYP1A2), bupropion hydroxylation (CYP2B6), diclofenac 4'-hydroxylation (CYP2C9), S-mephenytoin 4'-hydroxylation (CYP2C19), and testosterone 6 β -hydroxylation (CYP3A4/5 activity) were determined in microsomes prepared from the hepatocytes.

Results:

Treatment with the prototypical inducers (omeprazole, phenobarbital and rifampin) caused increases in CYP enzyme activities as expected (Table 1 & Figure 1). On average, omeprazole caused a 24-fold increase in phenacetin O-deethylase (CYP1A2) activity, phenobarbital caused a 19.7-fold increase in bupropion hydroxylase (CYP2B6) activity, while rifampin caused a 2.27-fold increase in diclofenac 4'-hydroxylase (CYP2C9) activity, an 8.84-fold increase in S-mephenytoin 4'-hydroxylase (CYP2C19) activity, and a 3.36-fold increase in testosterone 6 β -hydroxylase (CYP3A4) activity.

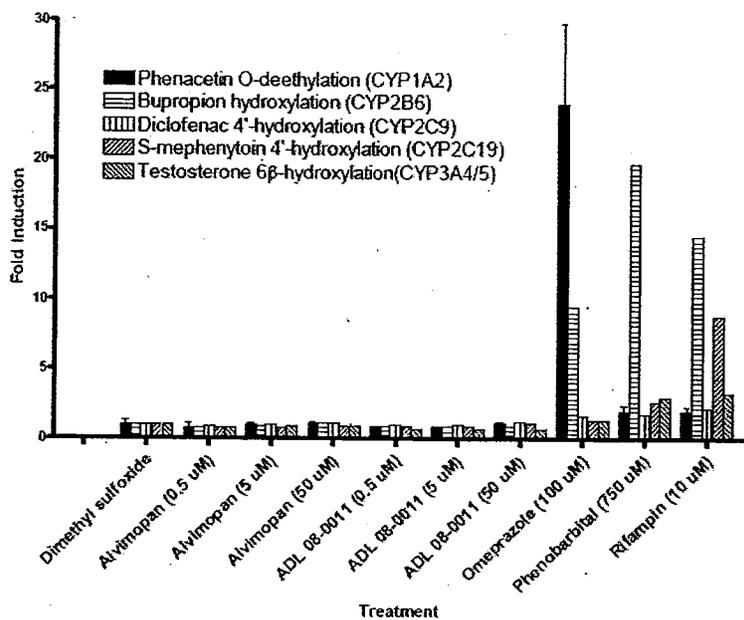
Treatment with alvimopan and ADL 08-0011 at concentrations of 0.5, 5, and 50 μM did not induce the catalytic activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 in primary cultures of human hepatocytes. The highest concentration used in this study (50 μM) was approximately 2500-fold and 500-fold greater than the mean peak plasma concentration of alvimopan and ADL 08-0011, respectively, following oral administration of alvimopan 12 mg twice daily.

Table 1: Effects of treating cultured human hepatocytes with Alvimopan, ADL 08-0011 or prototypical inducers on the expression of cytochrome P450 enzymes*

Treatment	Concentration	Enzymatic Activity (pmol/mg protein/min) ^a				
		Phenacetin O-deethylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Diclofenac 4'-hydroxylation (CYP2C9)	S-mephenytoin 4'-hydroxylation (CYP2C19)	Testosterone 6 β -hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	67.2 \pm 19.6	49.8 \pm 3.6	1110 \pm 400	23.9 \pm 23.7	4950 \pm 1190
Alvimopan	0.5 μ M	59.8 \pm 35.9	40.9 \pm 20.6	1060 \pm 640	19.9 \pm 21.0	3820 \pm 1490
Alvimopan	5 μ M	68.6 \pm 33.8	48.2 \pm 14.7	1070 \pm 180	17.9 \pm 15.0	4740 \pm 1830
Alvimopan	50 μ M	74.8 \pm 35.3	56.7 \pm 10.3	1230 \pm 360	20.1 \pm 18.2	4720 \pm 2440
ADL 08-0011	0.5 μ M	64.5 \pm 20.9	46.2 \pm 10.3	1130 \pm 420	21.1 \pm 18.8	3950 \pm 2210
ADL 08-0011	5 μ M	57.3 \pm 17.4	43.2 \pm 4.7	1090 \pm 370	19.2 \pm 16.3	3880 \pm 2490
ADL 08-0011	50 μ M	73.9 \pm 30.6	47.8 \pm 10.6	1400 \pm 500	27.2 \pm 27.0	3820 \pm 2500
Omeprazole	100 μ M	1640 \pm 640	475 \pm 215	1730 \pm 230	17.9 \pm 8.1	6680 \pm 4550
Phenobarbital	750 μ M	133 \pm 47	986 \pm 324	1880 \pm 450	45.1 \pm 27.5	14400 \pm 2900
Rifampin	10 μ M	133 \pm 17	731 \pm 297	2490 \pm 940	168 \pm 118	16200 \pm 1400

*Values are the mean \pm standard deviation of three human hepatocyte preparations

Figure 1: Effects of Treating Cultured Human Hepatocytes With Alvimopan, ADL 08-0011, or Prototypical Inducers on the Catalytic Activity of Cytochrome P450 Enzymes



Conclusion:

Neither alvimopan nor ADL 08-0011 is an inducer of CYP enzymes.

Bioequivalence Study

Protocol 14CL130: A Phase 1, Open-Label, Single-Dose, Two-Sequence Crossover Study to Determine the Bioequivalence of One Alvimopan 12 mg Capsule Relative to Two Alvimopan 6 mg Capsules in Healthy Male Subjects

Objectives:

The objective of this study was to assess the bioequivalence of one alvimopan 12 mg capsule relative to two 6 mg capsules as measured by the rate and extent of absorption of alvimopan in healthy male subjects.

Formulation:

The formulation of the 12 mg capsules is similar to that of the 6 mg capsules. The capsule formulations are simply alvimopan dispersed in PEG. The comparative components and composition information is listed in Table 2.

Table 2: Components and composition of Entereg Capsules

Components	Composition (mg/Tablet)	
	6-mg Capsules	12-mg Capsules
Alvimopan		12.0 ²
PEG		
Total Weight		300.0

¹ Equivalent to 6.0 mg on the anhydrous basis

² 12.0 mg on the anhydrous basis (The actual weight takes into account)

Methodology:

This study was an open-label, randomized, single dose, two-sequence crossover study. Eighty-eight eligible male subjects were enrolled and randomly assigned to one of two treatment sequences. Subjects received under fasting conditions single 12 mg doses of alvimopan with a 7- to 14-day washout separating the two treatment periods. During each dosing period subjects were to: (1) fast for at least 10 hours before and 4 hours after receiving alvimopan (while fasting, subjects were allowed to drink water ad lib except for 1 hour before and 1 hour after each dose; (2) drink 240 mL of water 30 minutes before each alvimopan dose (3) take each dose with 240 mL of water; and (4) have a 2200 calorie/day diet in accordance with the American Heart Association (AHA) diet at least 4 hours after administration of each dose.

Sixteen serial whole blood samples were collected to determine alvimopan plasma concentrations before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, and 36 hours after each dose.

Comments:

1. Subjects were required to take 240 mL of water 30 minutes before dosing and another 240 mL of water with each dose. This is a deviation from the conventional design for BE studies, in which water was allowed ad lib in all times except for the 240 mL of water at the time of dosing.
2. The individual PK parameters for the BE study should be submitted as an electronic file in a readily analyzable format.

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3. APPENDIX

APPENDIX 1: PHARMACOMETRICS REVIEW

NDA 21-775, Entereg

Pharmacometrics Reviewer: Joga Gobburu, Ph.D.

1 Introduction

There are two components to the pharmacometrics consult:

1. Review of the population PK report: The original population analysis report was reviewed by Dr. Sue-Chih Lee, Office of Clinical Pharmacology. The sponsor provided responses (see 24 Feb 2006 submission) to the comments provided by Dr. Lee. This pharmacometrics review will take into account the original comments and the sponsor's replies to provide recommendations pertaining to the proposed labeling statements.
2. Review of the QT report: Dr. Lee performed the original review of this study too. This pharmacometrics review will take into account the original comments and the sponsor's replies to provide recommendations pertaining to the QT prolongation potential of Entereg.

2 Population PK analysis

Summary of Sponsor's Analysis

Methodology:

Plasma concentration-time data, demographic data, and dosing data were combined from studies in healthy volunteers conducted by Adolor (Studies 14CL116, 14CL117, 14CL118, 14CL119, 14CL123, 14CL124, 14CL125, 14CL127, and 28CL201) and by GlaxoSmithKline (GSK) (Study SB-767905/016), as well as from studies conducted in patients with postoperative ileus (POI) by Adolor (Study 14CL308) and by GSK (Study SB-767905/001). Data were assembled from each of the clinical studies in which subjects received oral doses of alvimopan as one or more capsules, and a single comprehensive data set was formatted for analysis. Data analysis was performed using the nonlinear mixed-effects modeling program NONMEM (Version 5, Globomax Corporation, Baltimore, MD). Estimates were obtained for population mean parameters (typical values), standard errors of parameters, percent coefficient of variation, interindividual variability, and residual variability. An appropriate structural pharmacokinetic model was developed previously, based on review of the known and

plausible pharmacology of alvimopan and ADL 08-0011. The covariate model was then developed, on the basis of the plot of the ratio of observed to (population) predicted values, the objective function for each model and plots of the *posthoc* values for the pharmacokinetic parameters against covariates, in which systematic trends were sought. Each covariate whose inclusion was supported by the graphics was entered into the model, then backward elimination was used to delete nonsignificant covariates. The following covariates were pre-specified for inclusion in the analysis: age, weight, gender, height, body mass index (BMI), study number, food, alanine aminotransferase (ALT), aspartate aminotransferase (AST), dose, race: (Caucasian, African-American, Hispanic, other), obesity (a categorical variable coded as 0 [BMI ≤ 25]; 1 [25 < BMI ≤ 30], or 2 [BMI > 30]), and creatinine clearance (determined using the Cockcroft-Gault nomogram). The following covariates were also pre-specified for inclusion in the analysis:

Subject type: patients with Crohn's disease (Study 14CL125); surgical patients with inflammatory bowel disease (IBD) (Studies 14CL308 and SB-767905/001); volunteer subjects with mild, moderate, or severe renal impairment (Study 14CL116); subjects who had bowel resection, hysterectomy, radical hysterectomy, or other surgery (Studies 14CL308 and SB-767905/001); subjects in whom no surgery was performed (Studies 14CL308 SB-767905/001); healthy volunteers.

Assay: plasma assays were performed with a single validated liquid chromatography/mass spectrometry/mass spectrometry technique by two different vendors using several different lower limits of quantification (LLOQ): One assay was performed by [redacted] (LLOQ: 0.25 ng/mL) for some of the Adolor studies, and two assays were performed by [redacted] (one with an LLOQ of 0.1 ng/mL for Adolor studies and one with an LLOQ of 0.05 ng/mL for GSK studies).

Product source: Although the formulation and *in vitro* dissolution did not differ, there were three sources for the active pharmaceutical ingredients (APIs) used in these studies: [redacted] (Studies 14CL127, 14CL308, 28CL201, and SB-767905/016), [redacted] (SB-767905/001), and [redacted] (Studies 14CL116, 14CL117, 14CL118, 14CL119, 14CL123, 14CL124, and 14CL125).

Mechanical bowel preparation: patients who received one or more bowel preparations preoperatively (e.g., laxative, enema).

Preoperative antibiotics: patients who received at least one oral antibiotic preoperatively as part of their bowel preparation.

Perioperative antibiotics targeting gastrointestinal (GI) or skin microflora: oral or intravenous (IV) antibiotics with high activity against GI flora or those with high activity against skin microflora.

Gastric acid blocker use: histamine-2 blockers or proton pump inhibitors.

P-glycoprotein (PGP) inhibitor use: drugs known to inhibit PGP.

Results:

Alvimopan: Based on oral capsule data from all studies, a 2-compartment model, not normalized for body size, fit the data reasonably well. Typical values were 254 L/h for apparent oral clearance (CL/F), 1949 L for apparent oral volume of distribution at steady state (V_{ss}/F), 76.0 L/h for distributional clearance (CL_{distribution}/F), 1.03/h for absorption rate in the fasted state, and 0.422 h for lag time in the fasted state. Interindividual variability (expressed as a coefficient of variation) was moderate for absorption rate (60% in the fasted state) and for CL/F (56%) and was great for V_{ss}/F (68%) and CL_{distribution}/F (107%).

Covariate analysis: Covariate analysis was performed based on data from oral dosing only. As a result, all claims related to bioavailability may result from changes in either bioavailability or parallel changes in clearance, distributional clearance, and distribution volumes. Regardless, these effects on bioavailability indicate differences in plasma concentrations. There was no evidence that the pharmacokinetics of alvimopan vary as a function of weight, gender, height, BMI, obesity, IBD, renal function, AST, ALT, study number, assay, product source, concomitant antibiotic use, concomitant acid blocker use, or concomitant PGP inhibitor use.

Fed/Fasted: Food produced a 54% decrease in absorption rate and an 18% decrease in bioavailability in healthy volunteers.

POI patients: The extent of absorption was increased by 87% in POI patients (relative to healthy volunteers) in the fasted state. POI patients also had an 80% decrease in their rate of absorption in the fasted and fed state.

Age: Distributional clearance decreased by 1.0% per year of age and bioavailability in both the fasted and fed states decreased by 0.7% per year.

Dose: The bioavailability of the 24 mg dose was 19% lower than for all other doses (6-18 mg).

ADL 08-0011: Based on oral capsule data from all studies, a novel model fit the data well. This was a 1-compartment model with a time lag and a catenary chain to explain transport of alvimopan to the site of metabolism as well as its metabolism and systemic absorption. The term bioavailability (F) in the following section is based on the administered dose of alvimopan (i.e., it does not reflect the fraction of alvimopan absorbed systemically) and includes all events between the dosing of alvimopan and the appearance of ADL 08-0011 in plasma (e.g., the fraction of alvimopan metabolized to ADL 08-0011 and the fraction of ADL 08-0011 absorbed systemically). As with alvimopan, since only ADL 08-0011 data obtained after oral dosing of alvimopan was analyzed, a change in bioavailability may result from changes in either bioavailability or parallel changes in both clearance and volume. In addition, since the metabolite itself

was not administered, the true clearance and distribution volume of ADL 08-0011 cannot be determined. However, changes in CL/F and V/F can be used to describe overall changes in the plasma concentration-time profile for ADL 08-0011.

Typical values were 37.4 L/h for CL/F and 1240 L for V/F. In fasted subjects, lag time (time to first [nonzero] appearance of ADL 08-0011 in plasma following administration of alvimopan) was 1.15 hours (time to first quantifiable concentrations was much later), and mean transit time (MTT) was 22.7 hours. Variability for all of these parameters was great, consistent with the large variability in measured plasma concentrations, time to first measurable concentration, and time to peak concentration.

Covariate analysis: There was no evidence that the pharmacokinetic characteristics of ADL 08-0011 varied as a function of gender, height, dose, study number, ALT, AST, PGP inhibitors, assay, or product source.

POI Patients: Bioavailability (which includes all factors between dosing of alvimopan and appearance of metabolite in plasma) of ADL 08-0011 was 40% greater in POI patients than in healthy volunteers in the fasted state.

Fed vs. Fasted State: In fed subjects given alvimopan orally, bioavailability of ADL 08-0011 decreased by 25%, MTT increased by 49% (to 33.9 hours), and lag time increased by 408% (to 5.84 hours) compared with the fasted state.

Antibiotics: Bioavailability of ADL 08-0011 was 81% lower in patients receiving preoperative antibiotics. There was no effect of perioperative IV or oral antibiotics that target either GI microflora or skin microflora (although the number of subjects was small and the data were variable) on bioavailability.

Race: Bioavailability of ADL 08-0011 was 82% lower in Hispanics and 43% lower in African-Americans than that in Caucasians.

IBD: Bioavailability of ADL 08-0011 was 51% lower in patients with Inflammatory Bowel Disease (IBD) than in those without IBD.

Acid blockers: Bioavailability of ADL 08-0011 was 49% lower in patients receiving concomitant medications that block acid secretion.

United States (U.S.) vs. Rest of World: Bioavailability of ADL 08-0011 was 47% lower in those subjects studied outside the U.S. (Studies SB-767905/001 and SB-767905/016) than in those studied in the US. No other covariate explained this effect.

Conclusions:

- There was no evidence that the pharmacokinetics of alvimopan or ADL 08-0011 varied as a function of body size, BMI, gender, or renal function.

- There was no evidence that the pharmacokinetics of alvimopan or ADL 08-0011 varied as a function of mechanical bowel preparation or prior administration of PGP inhibitors.
- Food resulted in a decrease in the rate and extent of absorption of alvimopan and in the rate of formation/absorption of ADL 08-0011 in healthy volunteers.
- Concentrations of alvimopan were much higher (87%) and those of ADL 08-0011 were slightly higher (40%) in POI patients than in healthy volunteers. In addition, the rate of absorption of alvimopan and the rate of formation/absorption of ADL 08-0011 were slowed in POI patients.
- Increased age was associated with slightly higher concentrations of alvimopan (by approximately 30% - 40% in patients >70 years old over those in patients <30 years old); this effect was not important clinically based on the large variability in alvimopan pharmacokinetics.
- The pharmacokinetic characteristics of alvimopan were not affected by race. Plasma ADL 08-0011 concentrations were lower (by 43%) in black subjects and much lower (by 82%) in Hispanics following alvimopan administration. Plasma concentrations of ADL 08-0011 tended to be higher in subjects from the U.S. compared with those in subjects from the rest of world.
- The pharmacokinetics of alvimopan were not affected by concomitant administration of acid blockers or antibiotics. Plasma concentrations of ADL 08-0011 were lower (by 49%) in patients receiving acid blockers and much lower (by 81%) in subjects receiving preoperative antibiotics.

Summary of Dr. Lee's Comments and Sponsor's Responses

Dr. Lee, Office of Clinical Pharmacology, conveyed several comments to the sponsor regarding the population analyses. The sponsor provided responses to each of those comments, as shown in Table 1.

	Dr. Lee's comment	Sponsor response (see 24 Feb 2006 submission)
1	Volume of distribution at steady-state is overestimated by population analysis	Thus, the fact that the Vss after oral dosing is not as expected on IV data is related to differences in the detection limit and variability in rate of absorption and not necessarily to any issue related to the population PK model. Most importantly, the discrepancy does not invalidate the fit or usefulness of the population PK model. _____ _____

		Vss, which is based on noncompartmental and compartmental estimates of IV and oral dosing, to best describe the data.
2	Model fittings seem to be poor	Sponsor conducted an extensive validation procedure to substantiate the quality of the model.
3	Were the covariates tested on CL/F and Vss/F, before testing on bioavailability.	Sponsor included covariate effects on bioavailability only if it is at least as good as that on CL/F and/or Vss/F.
4	Range of creatinine clearance (CLcr) inappropriately includes values of 300 mL/min.	Various manipulations of the CLcr values (adjusting for BMI, truncation) yielded similar relationships with systemic CL of the drug.
5	Drug-drug interaction analysis should consider each (potentially) interacting drug (acid blockers, ppg inhibitors, antibiotics) separately.	Sponsor demonstrated that separate analysis by interacting drug yielded similar conclusions – that there are not meaningful interactions.
6	What are the implications of having varied distribution of demographics in each study on covariate modeling.	The main covariate that is varied across studies is race. The numbers of Blacks and Hispanics are reasonably well distributed among patients and healthy subjects.

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Current reviewer's Comments

- The following is the table of final parameter estimates for the parent model. Evidently, the bioavailability in patients was 87% higher than the healthy. Oral antibiotics did not affect the parent drug's exposure.

Parameter	Typical Value	Standard Error	Interindividual Variation (%) ^a
CL/F (L/hour)	254	12.7	56.0
V ₁ /F (L)	629	44.1	67.5 ^b
CL _{distribution} /F (L/hour)	76.0	7.15	107
Fractional change in CL _{distribution} per year of age (referenced to the value at 55 years)	-0.010	0.00220	—
V ₂ /F (L)	1320	122	67.5 ^b
F(fasted) ^c	1	—	—
Factor for bioavailability of the 24 mg dose compared to other doses (fasted only)	0.809	0.0614	—
Factor for F(fasted) in patients (Studies 14CL308 and SB-767905/001) compared to healthy subjects	1.87	0.143	—
F(fed) (expressed as a fraction of F(fasted)) ^d	0.825	—	—
Fractional change in F(fasted, fed) as a function of age (referenced to the value at 55 years)	-0.007	0.00163	—
k _s (fasted) (hour ⁻¹)	1.03	0.0734	60.0
k _s (fed) (hour ⁻¹)	0.470	0.0427	37.6
Factor for k _s (fasted) in patients (Studies 14CL308 and SB-767905/001) compared to healthy subjects	0.190	0.0158	—
Factor for k _s (fed) in patients (Studies 14CL308 and SB-767905/001) compared to healthy subjects	0.209	0.0567	—
Lag(fasted) (hours) ^d	0.422	0.00586	N.A.
Lag(fed) (hours) ^d	0.878	0.0194	N.A.

^a Computed as 100% * ω^2 , where ω^2 = variance(eta); 68% of the population lies within this range of the typical value.

^b Interindividual variability was applied to V_s; hence, the same term applies to each of V₁ and V₂.

^c F(fasted) was fixed to 1 for this analysis (see text); hence, no standard error is reported.

^d Interindividual variability was not permitted for this parameter.

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2. The following is the table of final parameter estimates for the metabolite model.

	Typical Value	Standard Error	Interindividual Variation (%) ^a
CL/F (L/kg/hour)	37.4	4.04	123
V/F (L)	1240	190	146
F(fasted) ^b	1.0	N.A.	N.A. ^c
Factor for F(fasted) in patients (Studies 14CL308 and SB-767905/001) compared with healthy subjects	1.40	0.384	—
F(fed)	0.753	0.112	N.A.
Factor for bioavailability for Hispanics	0.184	0.0831	—
Factor for bioavailability for African-Americans	0.573	0.0871	—
Factor for bioavailability for inflammatory bowel disease	0.489	0.176	—
Factor for bioavailability for preoperative antibiotics	0.195	0.0637	—
Factor for bioavailability for histamine-2 blockers	0.508	.0137	—
Factor for bioavailability for subjects in the ROW compared to U.S. subjects	0.531	0.0914	—
MTT (fasted) (hours)	22.7	2.33	377
MTT (fed) (hours)	33.9	4.73	114
Factor for <i>k</i> (fed) in patients (Studies 14CL308 and SB-767905/001) compared with healthy subjects	5.52	4.44	—
Lag(fasted) (hours) ^d	1.15	0.796	2334
Lag(fed) (hours) ^d	5.84	0.177	277

^a Computed as 100% * ω^2 , where ω^2 = variance(η); 68% of the population lies within this range of the typical value.

^b F(fasted) was fixed to 1 for this analysis (see text); hence, no standard error is reported.

^c Interindividual variability was not permitted for this parameter.

^d The lag time represents the time that concentrations are above 0, not above the detection limit. Because the metabolite is absorbed slowly (unlike alvimopan, which is absorbed much more rapidly), the time to quantifiable concentrations is likely to be later.

Evidently, the bioavailability of the metabolite was found to be 40% higher in patients in general. However, patients who received oral antibiotics had very low metabolite levels (~20%). This is attributed to the fact that antibiotics and/or pre-op procedures remove the microflora that are responsible for the metabolite formation.

3. This reviewer finds that the sponsor's responses to Dr. Lee's comments are reasonable.

3 QT Analysis

Summary of Sponsor's Analysis

Methodology: Study 016 was a parallel study of QT over time in healthy volunteers following: a single oral dose of Moxifloxacin 400 mg, multiple oral doses of Alvimopan 6 or 24 mg BID for 7 days, or multiple oral doses of placebo BID for 7 days. The methodology and results from the standard statistical approaches are described in detail

in the original clinical study report (HM2004/00274/00). The pertinent methodology for the PK/PD modelling of QT effects is summarized below.

Individual predicted plasma concentrations of alvimopan and metabolite were generated for each subject in Study SB767905/016 receiving alvimopan at the times of each ECG measurement using a previously developed population pharmacokinetic model for alvimopan (RM2005/00076/00). These data were combined with QT data from Study SB767905/016. The relationship between plasma concentrations and QT effects were evaluated via mixed effects modelling within the population analysis software NONMEM.

Number of subjects: 82 subjects receiving alvimopan and 41 subjects receiving placebo

Treatment administration: Subjects randomized to one of four treatment groups: (A) Alvimopan 6 mg PO BID (Days 1-7); (B) Alvimopan 24 mg PO BID (Days 1-7); (C) Moxifloxacin PO 400mg, single dose (Day 1 only); and (D) Placebo PO BID (Days 1-7)

Criteria for evaluation: ECGs suitable for QT analysis performed at: (A) Day 1: predose and at 1, 2, 3, 6 and 12h post-dose; (B) Day 7: pre-dose and at 1, 2, 3, 6, 12, 18, 23, 48 and 168h post-dose. A 12-Lead ECG for safety was taken on Day 1 (pre-dose) and at 2 and 12h post-dose, Day 4 (predose) and on Day 7 (pre-dose) and at 2 and 12h postdose.

Plasma concentrations of alvimopan and metabolite were predicted for all subjects in Study SB767905/016 receiving alvimopan at the times of each QT measured using the population pharmacokinetic model for alvimopan (RM2005/00076/00).

Statistical methods: The relationship between plasma concentrations and QT effects were evaluated using various linear models within NONMEM:

- Baseline model (with no correction for RR)
- Baseline model (with individual correction for RR)
- Slope related to alvimopan concentrations
- Slope related to metabolite concentrations
- Slope related to alvimopan and metabolite concentrations

Model exploration was performed via simulation. The QT effects (i.e., predicted change from baseline) for various concentrations (i.e., expected based on the distribution of concentrations after various doses of oral alvimopan) were simulated for 1000 patients using the final PK-PD model. The following scenarios were simulated and explored and summarized: (a) magnitude and distribution of the change from baseline at therapeutic concentrations in POI [C_{max} of alvimopan in POI patients receiving 12 mg in Study

SB767905/001 and Study 14CL308]; (b) magnitude and distribution of the change from baseline at therapeutic concentrations in OBD [C_{max} of alvimopan in OBD patients receiving 0.5 mg BID in Study SB767905/011]; and (c) the magnitude and distribution of the change from baseline at concentrations at the Lower Limit of the Model (2x_{BQL})

Summary:

There was a statistically significant relationship between QT (individually corrected for the RR interval) and alvimopan plasma concentrations. However, there was no clear/quantifiable relationship between QT (individually corrected for the RR interval) and metabolite concentrations. A linear model best described the relationship between alvimopan concentrations and QT.

The population mean estimate of baseline was 396 msec with a moderate degree of interindividual variability, as expressed by the SD of the variance of +/- 15 msec. The population mean slope correction factor on the RR interval was 0.36 (cf. 0.33 for Fridericia's correction) with a small degree of interindividual variability (CV%=10.3%). The effect of alvimopan concentrations on the lengthening of the QT interval following individual correction for the RR interval was relatively small, with a population mean estimate of 0.308 ms/ng/mL, with a moderate degree of interindividual variability, as expressed by the SD of the variance of ± 0.27 msec. PK/PD modeling and simulation showed that, on average, the mean increase in the POI and OBD patient populations would be less than 3 msec and less than 1 msec, respectively; these values are much less than that considered clinically meaningful (10 msec, on average).

In the worst case in the POI population (assuming the highest concentrations and the steepest slope and smallest RR correction factor), an individual could have a change from baseline of ~18 ms as a result of concentration-related effects (excluding residual variability; total effects including residual variability could be 36 msec, mean +/- 2xSD). Based on the model, a change of 18 msec could also be seen with placebo. Thus, the model is consistent with the observed data for alvimopan and placebo. Standard analyses showed that a similar number of subjects in Study SB767905/016 had changes in QT_{cF} of 30-60 msec at any time: 7 subjects receiving placebo, 5 subjects receiving alvimopan 6 mg (with one additional subject having a change of 61 msec very late in the profile), and 5 subjects receiving alvimopan 24 mg.

Simulations indicated that the % of patients predicted to have changes in QT with therapeutic concentrations in POI and OBD and with concentrations near the detection limit are similar; thus, while there is a statistical effect the magnitude is very small and not clinically relevant.

Conclusions:

- There is a very small, but quantifiable relationship between alvimopan concentrations and changes in the individual corrected QT interval.

- The relationship is unlikely to be clinically relevant in POI [redacted] because: the mean increase in the POI [redacted] patient populations would be less than 3 msec and less than 1 msec, respectively, values below the level of clinical or regulatory concern.
- In the worst case in POI, an individual could have a change from baseline of ~18 ms (excluding residual error) as a result of concentration-related effects, a value observed following placebo using standard statistical approaches.
- Simulations indicate that the % of patients predicted to have changes in QT with therapeutic concentrations in POI [redacted] and with concentrations near the detection limit are similar.
- There is no statistically significant or clinically relevant effect of metabolite concentrations on QT.

Current reviewer's Comments

1. Although there appears to be a statistically significant relationship between parent concentrations QTc prolongation, the slope of this relationship is shallow, as also noted by the sponsor.
2. The ICH E14 prescribed analysis renders the following results:

	Mean (upper 90% CI) QTc change corrected for baseline, placebo	
	6 mg	24 mg
Day 1	5.7 (9.9)	0.85 (5.0)
Day 7	5.8 (10.5)	5.9 (10.7)

The statistical analysis recommended by the ICH E14 document shows that at both 6 and 24 mg doses the upper 90% confidence interval only slightly exceeds 10 ms. More importantly, the lack of dose-response (compare 6 and 24 mg on both days) supports that the drug does not cause a notable QTc prolongation, consistent with the concentration-QTc relationship.

3. The sponsor proposed the following labeling under the section



**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sue Chih Lee
11/1/2006 02:53:54 PM
BIOPHARMACEUTICS

Abi Adebawale
11/2/2006 10:30:31 AM
BIOPHARMACEUTICS



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS (HFD-110)

Date: September 22, 2006

To: Eric Brodsky, M.D., Medical Officer
Tanya Clayton, B.S., Project Manager
Division of Gastroenterology, (HFD-180)

From: B. Nhi Beasley, Pharm.D., Clinical Reviewer

Through: Norman Stockbridge, M.D., Ph.D., Division Director

Subject: Approvability of alvimopan (Entereg®) capsules for postoperative ileus based on cardiovascular risk profile, NDA 21-775

Summary

This memo responds to your consult to us dated August 1, 2006, regarding the approvability of alvimopan for the postoperative ileus (POI) indication from a cardiovascular (CV) safety standpoint. The reason for the consult is because there were eight CV serious adverse events (SAEs) (7 MIs and 1 USA) in one opioid-induced bowel dysfunction (OBD) 52-week study; all in alvimopan treated patients. Unblinding of other CV SAEs in the OBD program resulted in a total of 12 on alvimopan and 3 on placebo. The OBD studies are still ongoing, so frequency of these events is unknown.

In the POI studies, out of 3,975 patients randomized (1,365 on placebo, 2,610 on alvimopan) there were 25 CV SAEs (MI, ischemia and angina) according to the sponsor. They occurred at a rate of 0.81%, 0.78% and 0.42 % in the placebo, 6 mg and 12 mg dose groups, respectively. The sponsor's data suggest that alvimopan short-term does not increase risk of an MI or ischemia. The reviewer's analysis of MIs shows that the event rate is 0.3%, 0.3%, and 0.5%, respectively (p-value NS for drug versus placebo). The relative risk of having an MI on 12 mg compared to placebo is 1.65 with a 95% CI of 0.59 to 5.48. The mean day of onset was around Day 6-7. However, the majority of patients experiencing an MI on alvimopan only received 1-2 doses. The reviewer concludes that the data do not suggest that alvimopan, for the indication of postoperative ileus, increases risk of major cardiovascular events.

Background

Alvimopan is an oral peripherally-acting mu-opioid receptor antagonist undergoing a second review cycle for POI in patients with bowel resection surgery. The proposed indication is to accelerate the time to recovery of both upper and lower GI function following bowel resection surgery. The proposed dosage is 12 mg orally prior to surgery, then BID for seven days after surgery. After the first review cycle, the safety profile of the 6 mg and 12 mg doses were acceptable.^{1,2} The most common treatment emergent adverse effects (TEAEs) were GI in nature and occurred with similar frequency between alvimopan and placebo groups. Because of insufficient evidence of effectiveness (low dose better than high, high dose better than low, and two failed studies), the sponsor submitted another study in May 2006 to substantiate the efficacy of the 12 mg dose. This study added 920 patients, making 3,975 the total number of POI patients randomized in the POI program.

In the interim, while studying alvimopan for OBD, eight serious cardiovascular events (7 MIs and 1 USA) occurred in the largest and longest duration study, Study 014, prompting a Glaxo Safety Board (GSB) review on April 27, 2006. One resulted in death. Study 014 is a 12 month treatment study that randomized (2:1, alvimopan 0.5 mg BID:placebo) 805 patients with OBD taking opioids for persistent non-cancer pain. After it was discovered that all eight CV SAEs occurred in alvimopan treated patients, the GSB unblinded all patients with CV SAEs in the OBD studies. This resulted in seven more patients (3 placebo and 4 alvimopan) with events that included MI, cardiac arrest, and sinus arrhythmia with non-specific ST elevation. There were a total of 2,955 patients studied in six OBD Phase 2b/3 clinical studies (n=2635) (4 in non-cancer pain and 2 in cancer pain) and nine smaller studies (n=320).

The sponsor attempted to collect more information on the 15 subjects with CV SAEs (See Table 1.). Of those patients enrolled in Study 014, three of the eight subjects were enrolled at one site in Glasgow, Scotland, and two of the eight subjects were enrolled at one site near Tampa, FL. Information on CV risk was not collected prospectively in any of the studies, so the risk assessment was incomplete in many patients. Notably, family history and medical history was often missing. The sponsor used prescription medications to conclude certain medical histories. While it seems that the longer duration of Study 014 might contribute to the higher number of events, six of the eight SAEs occurred within 90 days of treatment. Two of the other OBD studies were 90 days, and these two studies combined included 1,010 patients. Thus, duration does not appear to be a factor in the events.

Table 1. Description of patients experiencing serious myocardial event in OBD studies

	Study 14 (n=8)	Other OBD Studies (n=7)
Age	68 (47 – 93)	62 (43 – 91)
Male/female	3/5	3/4
≥ 2 CV risk factors¹	8	4
History of CAD¹	2	3
Duration of primary pain condition¹	14.9 years (9 – 20years)	6.6 years (0.9 – 10 years)
Duration of opioid analgesic use¹	12.3 years (1.33 – 22 years)	4.6 years (0.8 – 9 years)

Time of onset on drug	72 days (30 – 111 days)	10 days (1 – 33 days)
Time of onset on placebo	--	52 days (12-78 days)

Mean (range)

¹ Missing in some subjects

The sponsor submitted more detailed patient information on September 8, 2006 changing some of the initial diagnoses of myocardial events (See Table 2). The reviewer's adjudication of MI was made based on the standard definition (two out of three of the following: symptoms, ST segment elevations and enzyme elevations) and the sponsor's September 8 submission. After readjudication, there were only 6 MIs and 1 USA in Study 014. Thus, the CV event ratio in Study 014 was 3.5:0 for alvimopan:placebo or 3:0 for MI.

Table 2. Adjudication of patients initially classified as myocardial event in OBD studies (Excludes Study 014)

	MI (alv/pbo)	Ischemia/angina (alv/pbo)	Arrests (alv/pbo)	Afib (alv/pbo)
Sponsor's initial adjudication	3 (2/1)	2 (2/0)	2 (0/2)	
Reviewer's adjudication¹	2 (1/1)	1 (1/0)	2 (0/2)	1 (1/0)

¹ Patient Study 208-004-558, adjudicated by the sponsor as angina, experienced atypical chest pain, however it was relieved by SL NTG. ECG was negative, and information on enzymes was missing. Thus, not enough information was available to adjudicate.

Patient Study 011 – 1650 adjudicated as an MI was readjudicated as USA by investigator.

Patient Study 008 – 2474 adjudicated as ischemia was readjudicated as Afib based on the independent review of EKG and negative enzymes by the sponsor.

There were a total of 20 deaths in the OBD clinical program; four were associated with myocardial events. Two were termed "cardiac arrests" (both on alvimopan) and were not included in Table 2. These patients (Study 008, IDs 1346 and 1347) died in the setting of progressive metastatic cancer. The sponsor's September submission did not contain any more information to determine if these patients experienced an MI. The arrests in Table 2 consist of a sudden death (third death) and an arrest that survived. The fourth death is one that resulted from an MI (Study 014).

According to the sponsor's epidemiological interrogation of US data for elderly patients on chronic opioid therapy with ≥ 2 CV risk factors (medium risk population), the observed incidence rates of MI in the study patients is comparable (overlaps) to the expected rate in a medium CV risk population (cancer patients were excluded). The patients with CV events in Study 014 had significant CV disease history and the incidence rate in that trial alone was 6.4 MI/100 patient years. The relative risk of having a myocardial event was 1.7 (0.5 – 6.1) for alvimopan versus placebo.

Table 3. Myocardial event incidence per 100 patient years (95% CI) in alvimopan and placebo

	Alvimopan	Placebo
Study 14	6.4 (not provided)	NA
Pooled cumulative incidence rates across all OBD studies	3.6 (1.8 - 6.5)	2.1 (0.4 - 6.1)
Cumulative risk	11/1760 0.63% (0.31 - 1.12 %)	3/813 0.37% (0.08 - 1.07 %)
Expected incidence rate (medium risk population)	NA	1.7 (1.0 - 2.6)
Expected incidence rate (high risk population)	NA	10.5 (7.7 - 14.0)

The sponsor's investigation of the CV events concluded that the increased CV SAEs in Study 014 is unexplainable and due to random variation. The myocardial event rate across all OBD studies is consistent with the epidemiologic event rate in those with similar CV risk (based on the sponsor's epidemiologic analysis). The sponsor did not find a significant imbalance by treatment group with respect to the incidence of myocardial events in the Phase 2/3 OBD program. The sponsor did not find evidence of systemic selection bias favoring the randomization of a population at increased risk for CV disease or events in Study 014 compared to the other OBD studies. The overall demographics (age, race, body mass index, tobacco use and withdrawals) were somewhat similar between Studies 008, 011, 012, 013, and 014. The sponsor did not find evidence of CV risk associated with the use of opioid antagonists. Thus, the sponsor decided that all studies in OBD can continue, but with additional safety surveillance instituted.

To summarize, in almost 3,000 patients randomized in controlled OBD trials, there were 14 CV SAEs (ischemic in nature), of which eleven received alvimopan. Study 014 had the highest occurrence (6 MIs and 1 USA) that prompted a GSB to unblind all CV SAEs in the OBD studies. In the entire OBD program to date, there were a total of 8 MIs (7 on alvimopan and 1 on placebo), 2 angina (alvimopan) and 2 cardiac arrests (placebo). The studies have not been completely unblinded, so information on drug or placebo allocation in all patients is unknown.

The DCaRP has been consulted to specifically comment on the approvability of alvimopan for the POI indication from a cardiovascular safety standpoint given the possible cardiovascular signal in the OBD studies.

Plausible Rationale

There are two plausible hypothetical rationales for how an opioid antagonist may increase cardiovascular risk. First, although conflicting, there are some data that suggests that opioids protect the heart by indirect effects mediated by the autonomic nervous system (increased venous capacitance thus reducing preload, decreased systemic vascular resistance, leading to more efficient contractile response at lower ventricular volumes). The overall result is decreased cardiac oxygen consumption and an increased likelihood of meeting oxygen demands with available blood flow. The conflict comes from the CRUSADE study, a nonrandomized, retrospective review of observational data in nearly 57,000 patients that found nearly a 50%

increase in death in patients presenting with non-ST segment elevation that received concurrent morphine; nearly 17,000 received morphine.

Second, there is other evidence that opioids directly affect the opioid receptors by preconditioning the heart from ischemic injury. In artificially induced ischemia and reperfusion models, opioids prevented ischemic injury, as measured by infarct size. Treatment with opioid antagonists reversed this effect, and delta and kappa receptors mediate it. Mu and kappa opioid receptors have been found in the human myocardium.

The sponsor has not studied whether alvimopan reverses opioid induced myocardial preconditioning in animals. Alvimopan and its metabolite are selective for the mu receptor, but do have some affinity for other opiate receptors (See Table 4). The K_i of 0.4 nM and 0.8 nM correspond to a concentration of 0.2 ng/mL and 0.3 ng/mL, respectively. The sponsor states that the clinical concentrations of alvimopan and its metabolite make them unlikely to bind to the kappa and delta receptors.

Table 4. Binding affinity with cloned human mu opioid receptors

Receptor subtype	K_i (nM) Alvimopan	K_i (nM) Metabolite
Mu (μ)	0.44	0.81
Kappa (K)	10	110
Delta (D)	100	290

The sponsor's review of preclinical data failed to identify any signal suggesting a link between alvimopan and any cardiovascular abnormality (thrombogenic, vascular or hemodynamic). The Agency's pharm/tox reviewer reported no significant target organs of toxicity at sufficiently high doses; approval was recommended with no additional phase 4 commitments.

The reviewer's search of the literature for adverse cardiovascular events related to opioid antagonists found insufficient evidence to conclude that opioid antagonists increase cardiovascular events. One study in the literature suggests that naloxone, an opioid antagonist with less specificity for the mu receptor, can abolish adaptation to ischemia in humans after sequential coronary balloon inflations. The sponsor's search of the AERS database (up until Q3 2005) resulted in only 21 likely ischemic events out of a total of 999 AEs reported for naltrexone and naloxone, two nonselective opioid antagonists. However, there are obvious limitations to the AERS database.

Pharmacokinetics

Alvimopan is rapidly absorbed after oral administration with a median T_{max} of 2 hours and an absolute bioavailability of only 6%. Plasma concentrations of alvimopan increase proportionally with doses between 6 to 18 mg, and less than proportionally with doses between 18 to 24 mg. There is little accumulation of alvimopan with BID dosing. The half life ranges from 4-17 hours.

Concentrations of the metabolite are highly variable and it accumulates 6 to 9-fold after five days of dosing. The median T_{max} of the metabolite is 36 hours. Concentrations of the metabolite

remain constant for about 96 hours after the last dose and then decline with a half-life of 10-20 hours.

Review of cardiovascular safety of alvimopan in postoperative ileus (POI) patients

The nine Phase 2/3 POI studies evaluated 3,975 patients, 1,365 on placebo and 2,610 on alvimopan. All studies except one were conducted in the US and Canada. The dosage in most of the POI trials was 6 or 12 mg prior to surgery followed by 6 or 12 mg BID for seven days. The dose of 1-3 mg was also studied in 62 patients, but there were no CV SAEs. All doses were given while the patient was hospitalized except in Study 306.

The sponsor reports 25 patients experienced MI, ischemia or angina. These numbers were derived by adding those patients classified as “acute myocardial infarction”, “myocardial infarction”, age indeterminate myocardial infarction”, “myocardial ischaemia”, and “angina pectoris”. The sponsor later reported 7, 5 and 6 MIs, in placebo, 6 mg, and 12 mg doses, respectively; however “acute myocardial infarction”, “myocardial infarction”, and “myocardial ischaemia” patients were included in their definition of MI. The breakdown by dose is shown in Table 5.

Table 5. Selected Cardiovascular Treatment Emergent Adverse Events (TEAE) in the POI population

TEAE term	PBO (n=1365) n (%)	Alvimopan 6 mg (n=898) n (%)	Alvimopan 12 mg (n=1650) n (%)	Alvimopan Total (n=2610) n (%)
MI, Ischemia and angina	11 (0.8%)	7 (0.8)	7 (0.4)	14 (0.5)
MI (Sponsor 09.08.06)	7 (0.5)	5 (0.6)	6 (0.4)	11 (0.4)
MI (Reviewer confirmed)	3 (0.2)	1 (0.1)	8 (0.5)	10 (0.3)
MI (Reviewer confirmed and most likely)	4 (0.3)	3 (0.3)	8 (0.5)	11 (0.4)
AMI	0	1 (0.1)	1 (0.1)	2 (0.1)
MI	4 (0.3)	3 (0.3)	5 (0.3)	8 (0.3)
Age indeterminate MI	1 (0.1)	2 (0.2)	1 (0.1)	3 (0.1)
Myocardial ischaemia	3 (0.2)	1 (0.1)	0	1 (<0.1)
Angina pectoris	3 (0.2)	0	0	0
Cardiac arrest	3 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)
Chest pain	16 (1.2)	6 (0.7)	16 (1.0)	22 (0.8)
Blood pressure increased	11(0.8)	5 (0.6)	15 (0.9)	20 (0.8)
Syncope	4 (0.3)	1 (0.1)	8 (0.5)	9 (0.3)

¹ p>0.05 for treatment versus placebo

Except for the first row and reviewer's analysis, all other data extracted from Sponsor's Table A.2.4.2, pp 858 - 865 in the ISS. First row extracted from Table 11 in Sponsor's 05.16.06 submission.

Because of the more serious consequences of an MI over angina, the reviewer focused on the MI events. The reviewer's analysis was performed as follows. The May 2006 ISS SAS dataset was queried for those POI patients that were coded with "INFARCTION" in their AEDECODE (n=20). These patients included those coded as MI, AMI and age indeterminate MI. These patients were confirmed as having an MI if enough information was provided (CRF, narrative, symptoms, labs, ECG) (n=12). Three more patients were deemed as "most likely" if a specific MI was coded such as anterior, inferior or acute. There was insufficient information for 1 on placebo and 3 on 6 mg to appropriately adjudicate. One patient on 12 mg had ST depressions with nausea and vomiting, so the reviewer adjudicated this patient as angina (not MI).

The discrepancy between the reviewer and the sponsor with the number of MIs in the 12 mg dose might be explainable by the deaths since the sponsor adjudicated patients only once and to the worse event. Patient 13CL313-13-13015 and patient 14C1314-36-00240 (both on 12 mg) died subsequent to the MI, so it is possible that the sponsor counted these patients as a death, rather than an MI. However, these patients were included in Table 13 from the sponsor's May submission that includes all 25 patients allocated to "MI, ischemia and angina".

The discrepancy between the reviewer and the sponsor with the placebo and 6 mg dose is not as straightforward. The query of the SAS dataset results in 5 patients on placebo and 6 patients on 6 mg coded as an MI. It is possible to explain how a patient coded as an MI was really angina, but it is not as easy to explain who the two other subjects are that had an MI while on placebo (sponsor's adjudication).

The following terms used by the sponsor were not included in Table 5: cardiac failure, cardiac failure congestive, cardiopulmonary failure, cardio-respiratory arrest, electromechanical dissociation.

Although it was obvious that the events between placebo and alvimopan were not statistically different, the reviewer determined the relative risk of having an MI while on drug compared to placebo (Table 6). There were less events in the 6 mg dose group compared to placebo, thus the risk of having an MI was "reduced" on 6 mg alvimopan compared to placebo. Based on the reviewer's assessment of confirmed and most likely MIs, the risk of having an MI while on 12 mg is up to 5.5 fold higher than on placebo.

Table 6. Relative Risk (95 % CI) of having an MI on drug compared to placebo

	6 mg	12 mg
MI (Reviewer confirmed)	0.51 (0.05 – 4.86) p=1.0	2.21 (0.59 – 8.30) p=0.37
MI (Reviewer confirmed and most likely)	1.14 (0.26 – 5.08) p=1.0	1.65 (0.59 – 5.48) p=0.41
Sponsor	1.09 (0.33 – 3.24)	0.71 (0.25 – 2.01)

Fisher's Exact or X² p-value where appropriate

The POI population is an opioid naïve population who had an open laparotomy procedure such as a bowel resection (66%) or an abdominal hysterectomy. Approximately 72% of placebo subjects and 64% of alvimopan subjects had bowel resection. Mean age was around 58 and around 35% of patients were ≥ 65 years old. The mean duration of surgery and time between first dose and start of surgery were similar across treatment groups. The 20 patients in the MI population are described in Table 7. The earliest MI occurred on Day 1, while the latest occurred on Day 34. The time of onset in 8 patients out of 15 on drug occurred after only 1-2 doses of drug.

Table 7. Information on 20 patients allocated to MI by reviewer

Age (mean \pm SD)	67 \pm 9
M/F (n)	10/10
Alvimopan doses (1-2)	8
Alvimopan doses (≥ 5)	3
Alvimopan doses (no info)	4
Mi Onset (mean day)	
All	6.6
Exclude two¹	4.2
Placebo	4
Alvimopan	7.5
Alvimopan exclude two¹	4.3

¹ Two patients excluded had an MI on day 23 and 34.

Follow-up in the POI studies varied. In the six phase 3 studies, follow up after the last dose in 5-7 days by telephone call was used in 4 studies, in 104-14 days by telephone call in 1 study, and in 7-10 days by visit in 1 study.

There were 22 deaths; 11 from the original ISS and 11 additional deaths from the recent study. The breakdown is as follows: 9 placebo, 5 alvimopan 6 mg, 8 alvimopan 12 mg. The deaths in the alvimopan group were considered unrelated to drug. Ten of the 11 new deaths were in bowel resection patients and one was in a subject who did not have surgery.

Some CV risk profile information was recently submitted. There is no difference in these factors between placebo and alvimopan (Table 8).

Table 8. Percent of POI patients in all studies

	Placebo	Alvimopan
Age	58 \pm 14	57 \pm 15
Diabetes	20.0	21.6
HTN	48.5	45.0
Smoker	9.8	8.3
Obese (BMI ≥ 30)	32.2	29.1

Extracted from Table 1.1, page 4 submitted 09.13.06

Comparison of POI with OBD

The POI trials are of shorter duration (at most 7 days) and higher doses (up to 12 mg BID) than the OBD trials (most used up to 1 mg BID and were ≥ 6 weeks duration). The OBD patient population also includes cancer pain patients, who have other reasons for death, but not necessarily more reasons for having an MI. There was not much difference in age between the two groups. The incidence of MI was a little later in the OBD studies, however there were occurrences as early as Day 1 and the range on alvimopan in the other OBD studies was 1- 33 days, similar to that in the POI population.

Reports in healthy volunteers

Among healthy volunteers there were no deaths, no serious cardiovascular events, and one report of palpitations and chest pain (same patient).

Reviewer's conclusions

From a cardiovascular safety standpoint, there is no signal that alvimopan short-term increases the risk of cardiovascular events. Out of nearly 4,000 patients studied in POI, there were 4, 3, and 8 MIs in the placebo, 6 mg and 12 mg group, respectively. This corresponds to a rate of 0.3 %, 0.3% and 0.5%, respectively. The event rate on drug is not significantly different from placebo. There are not enough events to conclude that alvimopan used short-term increases the risk of MI and the data suggests that it does not. If the sponsor's definition of MI, ischemia and angina is used, then there were 11, 7, and 7 on placebo, 6 mg and 12 mg, respectively. This suggests that the events are higher on placebo. There is no signal by this definition either to suggest that alvimopan increases cardiovascular risk when used short-term.

Reviewer's comments

The sponsor should list and explain all patients adjudicated as MI and explain the discrepancy between the reviewer's and the sponsor's numbers.

The patients in Study 014 that experienced the events appear to be older than those that experienced the events in the other OBD studies. However, a comparison should be made with respect to demographics, CV history, and CV risk in both treatment and placebo group within study as well as between studies. Based on randomization, a difference within study is not expected. An overall comparison (treatment and placebo group combined) between studies should also be done.

According to the sponsor's epidemiologic study, they determined the incidence of AMI in patients on chronic opioid therapy by age, gender and CAD. However, in their analysis of myocardial events from the OBD studies, they included patients that also had ischemia/angina in the pool of AMI patients. This is technically incorrect and the analysis should be done using only AMI patients. Assuming the sponsor's numbers in the OBD studies are correct, a reanalysis would make the incidence rates lower.

Recommendation

From a cardiovascular safety standpoint, there is no signal that alvimopan short-term increases the risk of cardiovascular events. Please contact me or the Division if you have any further questions.

Documents Reviewed:

1. AE letter issued to the sponsor (06.21.05)
2. Memo from the Deputy Office Director to the sponsor (07.15.05)
3. ISS report and available patient narratives and crf's (05.09.06)
4. ISS data (05.09.06): A_AE.xpt and DISPOSIT.xpt. All POI studies (9) were included in the reviewer's analysis:

1	13C206
2	13C213
3	13C214
4	14CL302
5	14CL306
6	14CL308
7	14CL313
8	14CL314
9	GSK001

5. Glaxo Smith Kline review of myocardial ischemia in alvimopan long-term safety study 014. [REDACTED]
6. GI Medical Officer's review of alvimopan associated CV SAEs (05.16.06)
7. Glaxo Smith Kline response to 08.01.06 information request of CV SAEs [REDACTED]
8. Glaxo Smith Kline response to 09.06.06 information request (09.13.06)

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/s/

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07/11/05

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-775	Submission Date(s): 6/25/04, 10/22/04, 1/26/05, 5/19/05, 5/26/05, 6/7/05
Brand Name	Entereg
Generic Name	Alvimopan
Reviewer	Sue-Chih Lee, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
OND division	Division of Gastrointestinal & Coagulation Drug Products
Sponsor	Adolor (Exton, PA)
Submission Type; Code	1S
Formulation; Strength(s)	Capsules,
Proposed Dosing regimen	<ul style="list-style-type: none"> • 12 mg (2 capsules) at 30 min to 5 hrs prior to surgery • 12 mg BID beginning the day after surgery for a maximum of 7 days while the patient is hospitalized
Indication	To accelerate recovery of GI function following abdominal surgery

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1. EXECUTIVE SUMMARY

1.1 Recommendation

From the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, Human Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable provided that (i) a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert and (ii) the sponsor satisfactorily addresses the comments listed below.

1.2 Comments

1. The potential of alvimopan and ADL 08-0011 as CYP inducers should be evaluated with hepatocytes from at least 3 donors. (The studies conducted for alvimopan were inadequate and no studies were conducted for ADL 08-0011.)
2. The following comments pertain to the population PK analysis:
 - a. V_{ss}/F was estimated to be 1949 L from the population PK analysis, which is much higher than expected from a V_{ss} estimate of 30 L following IV administration and a F of <10%. The model does not seem to describe well the alvimopan pharmacokinetics.
 - b. Some covariates were found to impact on the fraction of drug absorbed (F). It is unclear whether the covariates were tested for their impact on CL (or CL/F).
 - c. Analysis on creatinine clearance may be inaccurate. It is noted that, in the population PK dataset, creatinine clearance (CL_{cr}) ranged up to >300 mL/min. In the calculation of CL_{cr} , adjustment may be made for subjects with high BMI. Alternatively, a maximum limit in CL_{cr} may be imposed in the population PK analysis. This, however, does not seem to have been done based on the control codes provided.
 - d. For analysis pertaining to drug-drug interactions, separate analysis should be performed for each drug. In addition, a table should be provided listing the number of patients on each dose.
 - e. It is noted that some covariates are concentrated in certain studies. [REDACTED] [REDACTED] the covariates should be further examined/tested to verify that samples size was adequate and that the impact of the covariate was not driven by one particular study.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Alvimopan (ADL 8-2698) is a μ -opioid receptor antagonist with no agonist activity. The inhibitory effects of opioids on gastrointestinal (GI) motility are considered to be primarily mediated through μ -opioid receptors located within the enteric nervous system. Alvimopan is intended to act peripherally without producing reversal of the desired, centrally mediated, analgesic effects of opioids.

Following oral administration of Entereg capsules, another compound, identified as ADL 08-0011, was found to be present in the plasma. ADL 08-0011 is an antagonist at the μ -receptor and is approximately equipotent to alvimopan in nonclinical models. In contrast to the relative

inability of alvimopan to antagonize the CNS effects of morphine, ADL 08-0011 has been demonstrated to antagonize morphine-induced analgesia in animal studies. This did not occur, however, until doses were 5-8-fold higher than those to reverse GI effects in the rat with intravenous (IV) administration.

In support of this NDA indication, the sponsor submitted four pivotal phase 3 efficacy trials (Studies 302, 308, 313 and 001) in patients undergoing bowel resection or hysterectomy. Note that Study 001 was submitted in April 2005, which extended the clock for 3 months. All four trials had 3 treatment arms comparing alvimopan 6 mg BID and 12 mg BID to placebo. The primary endpoint is time to recovery of GI function (GI^3), where $GI^3 = \max(\min(\text{flatus, BM}), \text{solid food})$. The sponsor has since ceased pursuing the indication in hysterectomy patients, leaving only one patient population (bowel resection patients). According to Dr. Sonia Castillo, Biometrician of DBE2, only one trial (#302) succeeded (i.e., was statistically significantly better than placebo) at 6 mg BID, and one trial (#313) succeeded at 12 mg BID. Currently, there is an efficacy trial (#314) ongoing in the U.S. comparing alvimopan 12 mg BID to placebo.

A Phase 2 trial (13C206) suggested that alvimopan 1 mg BID and 6 mg BID might be effective and another trial (Study 13C213) indicated that increasing the dose from 3 mg BID to either 6 mg BID or 12 mg BID did not improve the outcome. However, the higher doses (6 mg BID and 12 mg BID) were carried forward to Phase 3 trials as alvimopan appeared to have a wide margin of safety and dose titration would be clinically impractical. In the clinical trials, alvimopan was administered twice daily until hospital discharge or for 7 postoperative days. The most commonly observed adverse events were nausea and vomiting. In this application, the sponsor is seeking approval of the 12 mg BID regimen.

In a thorough QT study in healthy subjects, there appeared to be a dose-response relationship in QTc prolongation following multiple dose administration of alvimopan. However, the QT prolongation effect of alvimopan even at 24 mg BID is considered to be less than that of moxifloxacin 400 mg.

Entereg capsules are hard-gelatin capsules containing  of alvimopan on an anhydrous basis.

Pharmacokinetics

Alvimopan: Following oral administration to healthy adults, plasma alvimopan concentrations peaked at approximately 2 hours postdose and thereafter underwent a biphasic decline. No significant accumulation was observed after BID dosing. The terminal half-life ranged 10-14 hours. The pharmacokinetics of alvimopan was approximately linear after single or multiple doses of up to 18 mg and no further increase in exposure was found from 18 mg to 24 mg. Following 12 mg BID dosing, mean alvimopan C_{max} was 10.98±6.43 ng/mL and mean AUC_{0-12h} was 40.2±22.5 ng*h/mL.

ADL 08-0011: Concentration of ADL 08-0011 tended to rise slowly following oral administration of alvimopan capsules. Peak plasma concentrations occurred at 30-40 hours

postdose. After 4 1/2 days of BID dosing, concentrations of ADL 08-0011 were higher than those after the first dose but steady state was not reached. The terminal half life ranged 10-18 hrs. ADL 08-0011 AUC increased less than proportionally with increasing alvimopan dose. Following 12 mg BID dosing for 9 doses, mean ADL 08-0011 C_{max} was 35.73±35.29 ng/mL and mean AUC_{0-12h} was 706.2±789.4 ng*h/mL.

Even in healthy subjects, variability in PK parameters for alvimopan was high (CV~60%) and even higher for ADL 08-0011 (CV up to >100%).

Absorption and Food Effect

The absolute bioavailability of alvimopan from oral capsules was 6.0% (95% CI: 4.7-7.7%). High fat meal decreased the rate and extent of absorption of alvimopan (AUC: (20.8%; C_{max}: (38.0%) and prolonged the mean T_{max} (3.1 hr vs. 1.9 hr). The food effect on ADL 08-0011 exposure could not be accurately determined in the study due to inadequate sampling scheme.

Distribution

The (geometric) mean steady state volume of distribution (V_{ss}) was 30(10 L for alvimopan as determined following IV administration of alvimopan 12 mg.

Alvimopan was not highly bound to human plasma proteins (unbound: 19.5(2.0 %) and binding was concentration-independent over the range of 1 to 100 ng/mL. Binding was mostly to albumin and binding to human (1-acid glycoprotein was negligible (>99% free).

ADL 08-0011 exhibited a higher degree of protein binding than alvimopan (%unbound: 5.9±0.1) and binding was concentration-independent over the range of 10 to 500 ng/mL. Binding of ADL 08-0011 to 0.1% human α₁-acid was negligible (>90% free).

Metabolism

In a mass balance study, healthy subjects received a single oral dose of alvimopan 12 mg. An amide hydrolysis compound designated as ADL 08-0011 was identified in the urine (~6.0% of dose) and feces (~22% of dose). A glucuronide of ADL 08-0011 was also found in the urine (~1%). Additionally, an oxidative metabolite was present in the urine (~0.1% of dose) but its structure was not elucidated. It should be noted that ADL 08-0011 was also present in human plasma following IV administration of alvimopan but at lower concentrations compared to oral administration of the same alvimopan dose.

In vitro metabolism studies using human hepatocytes detected the oxidative metabolite but not ADL 08-0011. The sponsor postulates that ADL 08-0011 is formed by GI microflora through hydrolysis of the amide group in alvimopan. The source of alvimopan in the gut is either the unabsorbed alvimopan (bioavailability ~6%), or absorbed alvimopan that is subsequently secreted into the bile. This may be the reason for the delayed appearance of ADL 08-0011 in the

plasma (mean Tmax > 30 hours). The sponsor has some nonclinical data as listed below that are consistent with this hypothesis.

- a. Anaerobic incubation of alvimopan with stool showed that ADL 08-0011 concentrations increased with incubation time only in non-autoclaved stool samples and not in the autoclaved stool samples, suggesting that the bacterial flora in the stool can cause the formation of ADL 08-0011.
- b. Oral administration of radiolabeled alvimopan to bile duct cannulated dogs and rats found that substantial radioactivity was recovered in the bile, indicating alvimopan and/or its metabolites were secreted into the bile. In rats, however, the majority of radioactivity was found to be derived from a sulfate metabolite (which was not observed in humans) and a minor amount of radioactivity (<10%) was identified as alvimopan. This suggests that alvimopan may be secreted into the bile in humans.

Elimination

Approximately 2% of the administered alvimopan dose is excreted in the urine as the unchanged drug. Renal clearance of alvimopan accounts for approximately 30% of total plasma clearance. At this point, there is no evidence that hepatic metabolism is the primary route of alvimopan elimination. Biliary secretion may be important in the elimination of alvimopan, however, there is no direct evidence to confirm this.

Special Populations

Several studies were performed in special populations but most studies were not adequately designed. The sponsor conducted 2 population PK analyses. The results from the two analyses were somewhat different. The first analysis included only one Phase 3 trial which had only one sample per patient. The second analysis (submitted in late May 2005) included an additional Phase 3 trial with up to 7 samples per patient. Therefore, only the results from the second population PK analysis are described below. It is noted, however, that the population PK analysis has its weaknesses (see Section 1.2 for comments) and more information will be requested if the sponsor wishes to include the results in the label.

- Age: Bioavailability of alvimopan decreased by 0.7% per year in age.
- Gender: No effect on alvimopan or ADL 08-0011 PK.
- Weight: No effect on alvimopan or ADL 08-0011 PK.
- Race: Bioavailability of ADL 08-0011 was 82% lower in Hispanics and 43% lower in African-Americans than that in Caucasians.
- Renal impairment: No effect on alvimopan or ADL 08-0011 PK.
- POI patients: The bioavailability was increased by 87% for alvimopan and by 40% for ADL 08-0011 in POI patients.
- IBD patients: Bioavailability of ADL 08-0011 was 51% lower in patients with inflammatory bowel disease.
- Antibiotics: Bioavailability of ADL 08-0011 was 81% lower in patients receiving preoperative antibiotics. There was no effect of perioperative IV or oral antibiotics that target GI microflora or skin microflora on bioavailability.
- Concomitant acid blockers: Bioavailability of ADL 08-0011 was 49% lower.

Concomitant P-gp inhibitors: No effect

U.S. vs. other countries: Bioavailability of ADL 08-0011 was 47% lower in subjects studied outside of the U.S. than in those studied in the U.S.

The following are based on individual studies conducted by the sponsor.

Elderly: The sponsor conducted a study in 18 healthy elderly subjects. There are no matching young subjects in the study for direct comparison. Based on data obtained from other studies in young subjects, the age effect was not apparent.

Gender/Weight: There is no prospectively designed study to look at gender effect. An examination of Study 14CL123 (9 elderly males & 9 elderly females) indicated that alvimopan CL/F values in six females covered the same range as that in the nine males, with the other three females having somewhat higher CL/F values. Correction for weight would only worsen the differences between males and females.

Race: There is no prospectively designed study to look at the PK among different race.

Renal Insufficiency

The sponsor conducted a study in 24 subjects with various degrees of renal impairment (6 subjects in each of the four categories: normal, mild, moderate and severe impairment). There was no relationship between renal function and plasma alvimopan pharmacokinetics. On the other hand, ADL 08-0011 concentrations appeared higher in the moderate (mean AUC: ↑54%) to severe (mean AUC: ↑309%) renal impairment patients. High variability among subjects within a group of pre-specified renal insufficiency was observed, especially in the severe impairment patients (two severe impairment patients had very high ADL 08-0011 concentrations). Dosing in moderate and severe impairment patients should be based on clinical safety findings in these patients.

Hepatic Insufficiency

In Study 14CL117, 16 subjects with hepatic impairment (mild or moderate as determined by Child-Pugh Scores) were enrolled. In addition, each hepatic impairment group was matched with two normal subjects in age and weight. (The number of healthy subjects is 4 after pooling.) All subjects received a single 12 mg oral dose of alvimopan.

Although there is a trend towards higher exposure (AUC) in mild to moderate hepatic impairment patients, there is also a high degree of overlapping with healthy subjects. The number of subjects is too small, especially in view of the high variability. In another study in 3 patients with severe hepatic impairment, the results were very variable with two subjects behaving like normal volunteers while one had alvimopan exposure approximately six- to ten-fold of the other two. The effect of hepatic impairment may be related to certain impairment and not correlated with Child-Pugh scores.

Drug-Drug Interactions

The potential for metabolic drug-drug interactions appears low.

In vitro studies:

- Drug as a CYP substrate: no
- Drug as CYP inhibitor: no
- Drug as CYP inducer: no adequate studies for both alvimopan and ADL 08-0011
- Drug as P-gp substrates: yes, based on a study using Caco-2 cells
- Drug as P-gp inhibitor: no, based on a study using MDCKII cells. (The basolateral to apical transport of digoxin was not affected by alvimopan or ADL 08-0011.)

In vivo study:

The sponsor conducted a drug interaction study with morphine. Administration of morphine sulfate IV 2 hours following oral administration of alvimopan reduced morphine bioavailability (AUC: ↓17%) but did not appear to change the plasma concentrations of morphine glucuronide (a metabolite of morphine). In Phase 3 trials, there was no evidence of dose creeping in patients taking morphine for pain relief.

Dosage Adjustment/Dosing Recommendations

High variability in the pharmacokinetics of both alvimopan and ADL 08-0011 was observed. Scatter plots were made to compare PK parameters obtained from various Phase I studies. It was found that there was extensive overlapping in PK parameter values for all special populations studied as compared to healthy subjects. It should be noted that higher alvimopan exposure (C_{max} and AUC) was observed in one patient with severe hepatic impairment (>5x of average exposure in healthy subjects) and two patients with quiescent Crohn's disease (3x of average exposure in healthy subjects). For ADL 08-0011, two severe renal impairment patients had high exposures (8-12x of average exposure in healthy subjects). These observations have been communicated to Dr. Eric Brodsky, Medical Officer of HFD-180.

Even when there are significant changes in PK due to intrinsic (e.g., race) or extrinsic factors, dosage adjustment will have to take the following points into consideration.

(1) If the drug activity is derived from local action: According to Dr. Tamal Chakroborti, Pharmacologist of HFD-180, alvimopan (or ADL 08-0011) does not have to be absorbed to exert its action since μ -receptors are distributed throughout the GI tract. If this is the case, the drug concentration in the GI tract would be important and what happens to the plasma concentration may not reflect the efficacy. Dosage reduction for patient with higher plasma concentrations may be detrimental to efficacy, especially when the drug is considered safe. In case of lower plasma concentrations, efficacy may not be affected and there is no need to increase the dose. (Note that both the parent compound and ADL 08-0011 are considered relatively safe, according to Drs. Eric Brodsky and Tamal Chakroborti, Medical Officer and Pharmacologist of HFD-180.)

(2) If the drug works through both local and systemic actions: The relative contribution by either route cannot be quantified. Additionally, the relative contribution by either the parent or ADL 08-0011 is also unknown. The situation is further complicated when the parent drug concentrations are increased but not the ADL 08-0011 concentrations or vice versa. Under such circumstances, there is no rational approach for dosage adjustment based on PK. PK is useful in

identifying the subpopulations for special considerations but clinical safety and efficacy information will be the primary basis for dosage adjustment.

Dosing in special populations will be considered when the efficacy of the drug product is demonstrated.

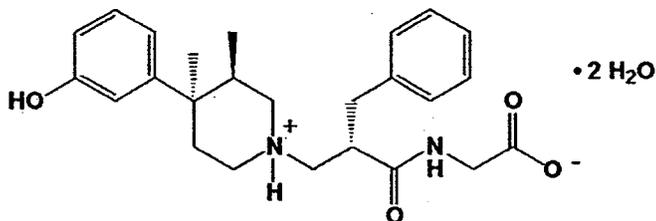
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

A. Drug Substance

Alvimopan is a white to light beige powder. The chemical name is N-[(2S)-2-[[[(3R,4R)-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]glycine dihydrate with an empirical formula of $C_{25}H_{32}N_2O_4 \cdot 2H_2O$ and a molecular weight of 460.6. At neutral pH, alvimopan is zwitterionic as shown below.



Alvimopan is slightly soluble in ethanol (5-10 mg/mL). The _____ of alvimopan varies with pH.

pH 1.2: _____

pH 3.0 - 9.0: _____

0.1N NaOH: _____

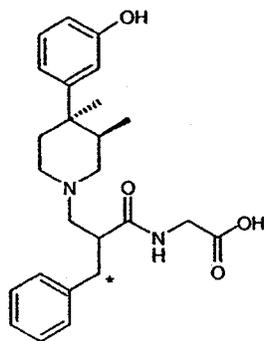
B. Formulation

The unit dose composition of alvimopan capsules is shown in the table below:

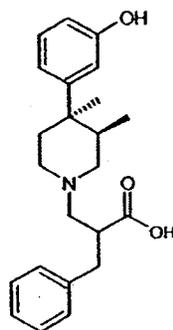
Ingredient	mg/capsule
Alvimopan ¹	_____
Polyethylene Glycol _____	_____
_____	1 capsule
Total Fill weight	300.0

2.1.2 What is the proposed mechanism of action?

Alvimopan (ADL 8-2698) is a μ -opioid receptor antagonist with no agonist activity. In humans (and animals) given alvimopan, ADL 08-0011 (the amide hydrolysis compound) is also present in the plasma. In nonclinical studies, ADL 08-0011 was of similar potency to alvimopan at the μ -opioid receptor and was a more selective μ receptor antagonist than alvimopan. The K_i value for antagonism of [3 H]diprenorphine binding to the cloned human μ receptors was 0.44 nM for alvimopan and 0.81 nM for ADL 08-0011.



Alvimopan
(ADL 8-2698)



Amide hydrolysis compound
(ADL 08-0011)

The inhibitory effects of opioids on GI motility are primarily mediated through μ -opioid receptors located within the enteric nervous system. The drug product is intended to act peripherally without producing significant reversal of the desired, centrally mediated, analgesic effects of opioids.

2.2 General Clinical Pharmacology

2.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The Phase 3 clinical trials enrolled patients who were scheduled to undergo bowel resection (BR) or total hysterectomy (TAH). The primary clinical endpoint in the Phase 3 efficacy studies was the time to recovery of GI function (or resolution of POI). Achieving this endpoint required the recovery of both upper and lower GI function. Recovery of upper GI function was defined as the time, following the end of surgery (last suture or staple), to tolerating solid food for the first time. Recovery of lower GI function was defined as the time, following the end of surgery, to first experiencing flatus or bowel movement (BM), whichever occurred first. These events were closely monitored postoperatively and were, in most cases, a main determinant of a patient's readiness for hospital discharge. Thus, this primary endpoint is a three component composite endpoint, referred to as "GI³." Mathematically, it can be expressed as follows:

$$\text{Time to recovery of GI function (GI}^3\text{)} = \max (\min(\text{flatus, BM}), \text{solid food})$$

Several secondary endpoints were determined in the Phase 3 studies:

- *Time to tolerating first solid food and time to first BM*, whichever occurred last, referred to as GI²: this endpoint was added because flatus was considered a less objective measure.
- *Time to readiness for hospital discharge based solely upon the recovery of GI function*: this measure may impact patient care cost.
- *Time to hospital discharge order written*: this measure is directly related to patient care cost.
- *Time to First Tolerating Solid Food; Time to First Flatus; Time to First Bowel Movement*: as separate measures
- *Proportion of Responders*: A responder was defined as any subject who achieved the primary endpoint within 108 hours post BR or radical TAH, or within 60 hours post simple TAH.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, if no inversion of chiral centers occurred *in vivo*. Both alvimopan and ADL 08-0011 concentrations in the plasma (and urine, in some studies) samples were determined using validated LC/MS/MS assay methods. It is noted that alvimopan molecule has three chiral centers. The sponsor did not conduct any study to demonstrate that no inversion of chiral centers occurred following oral administration of alvimopan.

Exposure-Response Evaluations

2.2.3 What are the characteristics of the exposure-response relationships for efficacy?

There is no clear exposure-response relationship for efficacy.

Dose-Response:

The sponsor has conducted five efficacy trials (4 completed and 1 still ongoing) in bowel resection or hysterectomy patients. However, the proposed indication has since been limited to bowel resection patients because of evidence showing lack of efficacy in hysterectomy patients.

Table 1 was provided by Dr. Sonia Castillo, Biometrician of DBE2. Based on median time to recovery of GI function, there was no clear dose response relationship.

**Table 1: Results for Four Phase 3 Trials of Alvimopan for Bowel Resection Patients
(Primary Efficacy Endpoint: GI³)**

Study	N	Censored N (%)	Median ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
14CL302					
Placebo	99	9 (9.1)	108.3(95.9,116.2)		
Alvimopan 6 mg	99	7 (7.1)	93.3 (87.3, 98.2)	1.48 (1.10, 1.98)	0.009*
Alvimopan 12 mg	98	9 (9.2)	97.5 (94.0, 104.1)	1.30 (0.96, 1.74)	0.086
14CL308					
Placebo	142	13 (9.2)	109.8(98.8,118.8)		
Alvimopan 6 mg	137	9 (6.6)	104.5(98.0,116.3)	1.22 (0.96, 1.56)	0.106
Alvimopan 12 mg	139	14 (10.1)	98.0 (94.2, 103.8)	1.32 (1.03, 1.68)	0.029
14CL313					
Placebo	142	24 (16.9)	98.9 (92.1, 115.1)		
Alvimopan 6 mg	149	15 (10.1)	96.5 (94.6, 103.4)	1.25 (0.97, 1.60)	0.084
Alvimopan 12 mg	160	16 (10.0)	94.1 (87.9, 99.7)	1.49 (1.17, 1.91)	0.002*
SB767905/001					
Placebo	229	19 (8)	81.7 (75.7, 89.8)		
Alvimopan 6 mg	237	18 (8)	73.8 (71.2, 77.7)	1.22 (1.01, 1.47)	0.042
Alvimopan 12 mg	238	19 (8)	78.5 (73.8, 86.2)	1.13 (0.94, 1.37)	0.200

Source: Statistical Reviewer's (Sonia Castillo, Ph.D., Div. Of Biometrics 2) analysis.

^a Estimate (in hours) was calculated from the Kaplan-Meier survival curve.

^b Hazard ratio of alvimopan to placebo was calculated from a Cox proportional hazards model that included treatment.

^c p-value was calculated from the Wald Chi-square tests for pair-wise comparisons between alvimopan and placebo from the Cox proportional hazards model noted above.

* Statistical significance at the 0.05 level after adjustment for multiple comparisons using the Hochberg method.

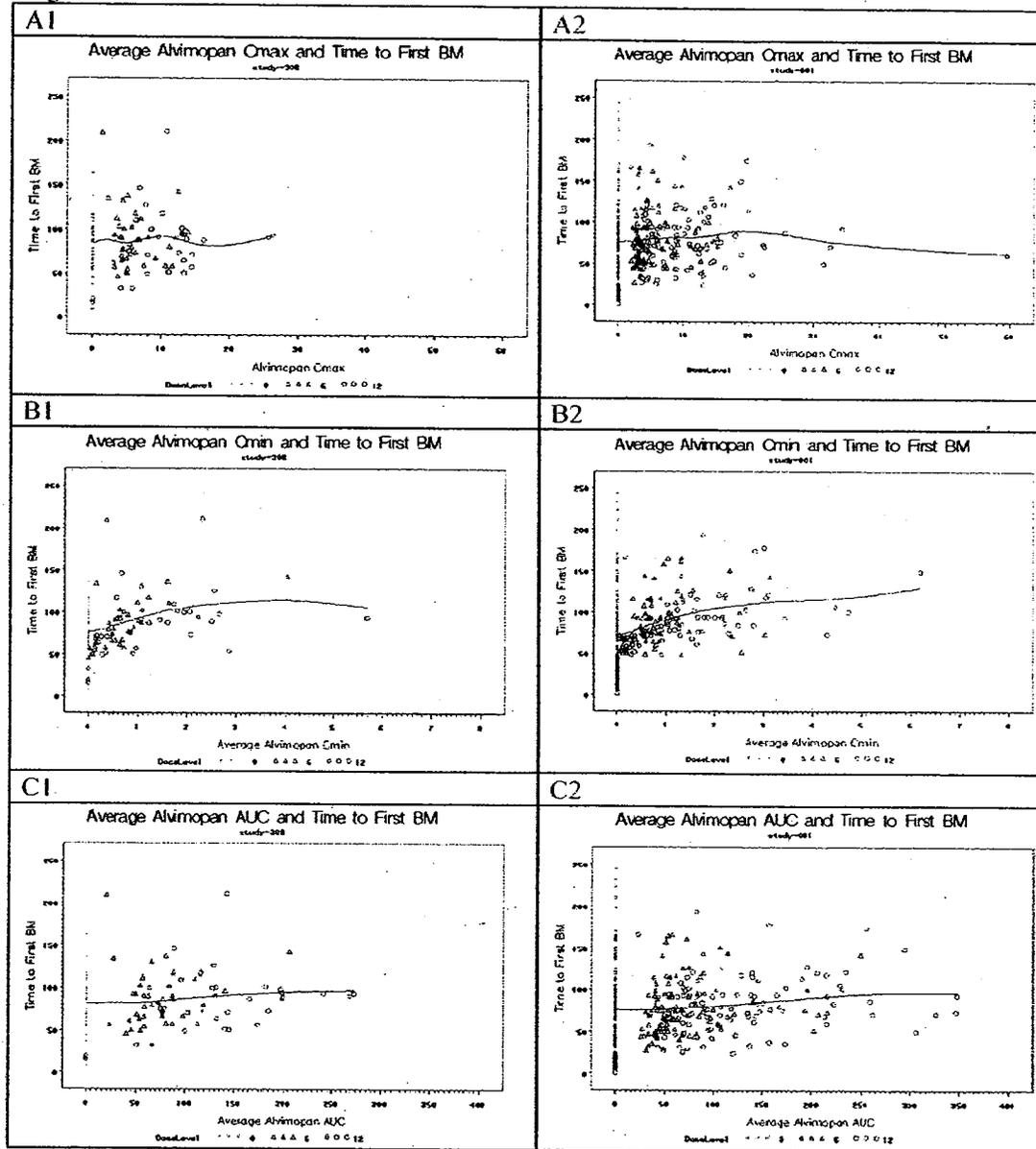
Concentration-Response:

The sponsor conducted a population PK/PD analysis using data obtained from 766 patients with postoperative ileus in two Phase 3 trials (Studies 14CL308 and SB-767905/001). In an attempt to minimize variability in the outcome measure, a different PD measure (time to first BM) was used in this analysis. Exposure measures selected were C_{min}, C_{max}, AUC, and FxGTki (fraction of time when plasma concentrations were above k_i) on various treatment days. Active species considered were alvimopan alone, ADL 08-0011 (SB-791399) alone, and combination of the two above (after adjustment for k_i and protein binding). The analysis considered different patient populations (all patients, bowel resection patients only, or hysterectomy patients only).

However, no clear exposure-response relationship was identified (Fig. 1 for alvimopan). A weak trend was found for average AUC of ADL 08-0011 being higher in subjects with a longer time to first BM. This delayed time to BM is considered by the sponsor to result in an increased residence time for alvimopan in the gastrointestinal (GI) tract, leading to increased metabolism of alvimopan to ADL 08-0011 by GI microflora. The reversed cause-effect relationship (i.e., higher AUC of ADL 08-0011 resulted in longer time to BM) is considered unlikely. In Study 14CL308, the sampling scheme (1 sample/subject) may limit the reliability of the analysis. However, no concentration-response relationship was found with Study SB-767905/001 either,

which had an improved sampling scheme. It should be noted that there are issues with the population PK analysis that the sponsor needs to address.

Fig. 1: Examination of exposure-response (time to 1st BM) relationship for alvimopan in bowel resection patients



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2.2.4 What are the characteristics of the exposure-response relationships for safety?

In Phase 3 trials, the frequency of treatment-emergent adverse events were similar among the three treatment groups (placebo, 6 mg BID and 12 mg BID) (Table 2) except for urinary retention. The most frequently reported events were nausea (~60%) and vomiting (~25%), which were most likely the results of surgery procedures. No increase in serious adverse events

was observed at higher alvimopan dose. Some adverse events occurred less frequently in the alvimopan groups (e.g. pulmonary complications).

Table 2: Treatment-emergent adverse events in three Phase 3 trials

	Overall POI N (%)			Bowel Resection N (%)			Abdominal Hysterectomy N (%)		
	Alvimopan			Alvimopan			Placebo (N=291)	6 mg (N=165)	12 mg (N=569)
	Placebo (N=748)	6 mg (N=604)	12 mg (N=1024)	Placebo (N=426)	6 mg (N=416)	12 mg (N=429)			
Nausea	461 (61.6)	340 (56.3)	639 (62.4)	257 (60.3)	223 (53.6)	220 (51.3)	188 (64.6)	108 (65.5)	408 (71.7)
Vomiting NOS	198 (26.5)	135 (22.4)	246 (24.0)	111 (26.1)	94 (22.6)	83 (19.3)	79 (27.1)	40 (24.2)	159 (27.9)
Abdominal distension	109 (14.6)	76 (12.6)	115 (11.2)	70 (16.4)	56 (13.5)	60 (14.0)	38 (13.1)	20 (12.1)	53 (9.3)
Pruritis NOS	94 (12.6)	70 (11.6)	116 (11.3)	56 (13.1)	46 (11.1)	39 (9.1)	36 (12.4)	20 (12.1)	75 (13.2)
Post-procedural pain	27 (3.6)	27 (4.5)	26 (2.5)	11 (2.6)	16 (3.8)	8 (1.9)	16 (5.5)	10 (6.1)	17 (3.0)
Urinary retention	17 (2.3)	19 (3.1)	41 (4.0)	9 (2.1)	15 (3.6)	19 (4.4)	7 (2.4)	4 (2.4)	22 (3.9)
POI	71 (9.5)	41 (6.8)	42 (4.1)	58 (13.6)	30 (7.2)	36 (8.4)	12 (4.1)	8 (4.8)	6 (1.1)
Pulmonary complications (%) ^a	15.1%	10.8%	8.4%	13.8%	10.1%	10.5%	16.2%	12.7%	6.7%

2.2.5 Does this drug prolong the QTc interval?

In the formal QT study, there was some trend of increase in QTcF with alvimopan dose. However, the increase does not appear to be as apparent as moxifloxacin 400 mg even at high alvimopan dose (24 mg BID).

The formal QT study was conducted in healthy subjects, which was of a randomized, placebo-controlled, parallel-group design. Both alvimopan and placebo were administered under double-blind conditions and moxifloxacin under open-label conditions. A total of 162 subjects completed the study (age: 18-56 yrs; wt: 45.5-97.0 kg; Caucasian: 89%; Black:4%; male: 44%; female: 56%).

The treatments were: A: Alvimopan 6 mg bid (Days 1-7*); N=46
 B: Alvimopan 24 mg bid (Days 1-7*); N=45
 C: Moxifloxacin 400mg od (Day 1 only); N=46
 D: Placebo bid (Days 1-7*); N=45
 *Day 7: morning dose only

ECG measurements were collected pre-dose and at 1, 2, 3, 6 and 12h post-dose on Day 1, and pre-dose and at 1, 2, 3, 6, 12, 18, 23, 48 and 168h post-dose relative to Day 7 dose. PK samples for assay of alvimopan and ADL 08-0011 were also collected. Increasing alvimopan dose from 6 mg BID to 24 mg BID increased the geometric mean AUC(0- τ), C_{max} and C_{min} to 3.8-fold, 4.1-fold and 3.4-fold, respectively.

QTc change from baseline:

The sponsor's analyses focused on QT data at 2 hr postdose on Day 1 (to capture the population T_{max} for both moxifloxacin and alvimopan), and at 2 h and 12 h postdose on Day 7 (T_{max} for alvimopan and possibly ADL 08-0011, respectively). The mean change in Fredericia-corrected QT values for moxifloxacin was 9.8 msec after baseline adjustment and placebo correction, indicating that the study had the sensitivity to detect important changes in QT (Table 3). Based on the sponsor's analyses at the specified time points, there was no signal of QT prolongation following multiple dose administration of alvimopan even at 24 mg BID.

Table 3: Summary of baseline-adjusted, placebo-corrected mean (range) QTcF

Measurement Time	Alvimopan 6 mg bid (N=46)	Alvimopan 12 mg bid (N=45)	Moxifloxacin 400 mg (N=46)	Inter-subject Variability*, ms
Day 1, 2 h postdose	0.35 (-3.65, 4.35)	0.37 (-3.67, 4.41)	9.77 (5.76, 13.78)	11.0
Day 7, 2 h postdose	-0.42 (-5.27, 4.44)	2.84 (-2.14, 7.81)	-	13.0
Day 7, 12 h postdose	3.04 (-1.17, 7.25)	-0.46 (-4.79, 3.87)	-	11.3

*CVb(%) = $\sqrt{\exp(\text{MSE}) - 1}$ * 100, where MSE is the mean square error from the ANOVA.

**Placebo, N=45.

An analysis of the full QT profile revealed a trend of increase in QT with alvimopan dose in both the change in QTcF and outlier analysis, especially for the Day 7 data. The study did not have a treatment arm of moxifloxacin on Day 7 for direct comparison. However, it is believed that the QT prolongation effect was less than moxifloxacin even at the alvimopan dose of 24 mg BID (Tables 4A & 4B).

Table 4A: Δ QTc for all treatments on Days 1 & 7

Treatment	# of Subj.	Δ QTcB Mean \pm SD (msec)	Δ QTcF Mean \pm SD (msec)
<i>Day 1</i>			
A	42	10.56 \pm 14.35	3.48 \pm 10.39
B	41	7.83 \pm 18.79	1.72 \pm 11.65
C	42	12.39 \pm 17.21	10.99 \pm 12.22
D	41	5.52 \pm 15.14	1.33 \pm 10.19
<i>Day 7</i>			
A	42	8.19 \pm 15.24	7.06 \pm 13.75
B	38	6.99 \pm 20.96	10.01 \pm 13.89
D	39	0.59 \pm 14.57	4.99 \pm 11.73

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Table 4B: Outlier analysis for all treatments on Days 1 & 7.

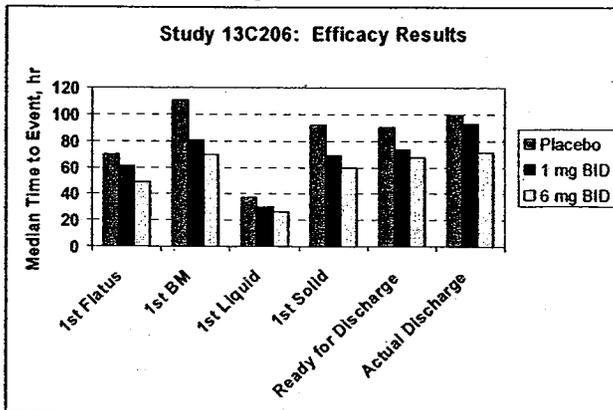
Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
<i>Day 1, ΔQTcF: 30-60 msec</i>						
A	42	11	26.19	617	15	2.43
B	41	13	31.71	610	20	3.28
C	42	17	40.48	613	44	7.18
D	41	9	21.95	608	13	2.14
<i>Day 1, ΔQTcF: >60 msec</i>						
A	42	0	0.00	617	0	0.00
B	41	0	0.00	610	0	0.00
C	42	1	2.38	613	1	0.16
D	41	0	0.00	608	0	0.00
<i>Day 7, ΔQTcF: 30-60 msec</i>						
A	42	12	28.57	1106	27	2.44
B	38	19	50.00	1012	60	5.93
D	39	8	20.51	1031	15	1.45
<i>Day 7, ΔQTcF: >60 msec</i>						
A	42	3	7.14	1106	3	0.27
B	38	3	7.89	1012	3	0.30
D	39	0	0.00	1031	0	0.00

2.2.6 What is the rationale for the dose selection?

The proposed dosing regimen is 12 mg at 30 min to 5 hrs prior to surgery followed by 12 mg BID beginning the day after surgery for a maximum of 7 days while the patient is hospitalized.

Three Phase 2 trials of alvimopan for the management of POI were conducted. The first trial (#13C206) included three treatments (alvimopan 1 mg BID, alvimopan 6 mg BID and placebo; total N=79) and alvimopan 6 mg BID appeared more effective than 1 mg BID (Fig. 2).

Fig. 2



A second Phase 2 trial (Study 13C213) showed that 3 mg BID was significantly better than the placebo and increasing the dose to 6 mg BID and 12 mg BID did not improve the outcome. The third trial (13C214) showed that improvement over placebo in time to GI recovery for the 12 mg BID treatment arm did not reach statistical significance. However, the higher doses (6 mg BID and 12 mg BID) were carried forward to Phase 3 trials as alvimopan appeared to have a wide margin of safety and dose titration would be clinically impractical.

According to Dr. Eric Brodsky, Medical Officer of HFD-180, safety data obtained from Phase 3 trials (4 efficacy and 1 safety trials) also showed no particular safety concern even at 12 mg BID. In addition, patients on alvimopan did not receive higher doses of opiate, suggesting that the analgesic activity was not reversed by the administration of alvimopan. At this point, however, it appears that the efficacy of alvimopan for POI has not been clearly demonstrated. Out of 4 Phase 3 efficacy trials, only one trial showed that alvimopan was statistically significantly better than placebo at 6 mg BID, and another trial at 12 mg BID (see Table 1). There is an ongoing Phase 3 efficacy trial in the U.S., which compares two treatment arms (12 mg BID vs. placebo).

PHARMACOKINETICS

2.2.7 What are the single- and multiple-dose PK parameters following oral administration of alvimopan in healthy subjects?

Study 14CL119 was of a parallel design with five treatments (placebo and 4 alvimopan dose levels: 6 mg, 12 mg, 18 mg, and 24 mg). A total of 40 subjects participated in the study (age: 21-67 yrs; wt: 68.0-98.4 kg; 33 males & 7 females; 33 Caucasians, 5 Blacks, 1 Hispanic & 1 Other). A single dose of alvimopan or matching placebo was administered after a minimum 6-hour fast (nothing by mouth) on the morning of Day 1 and Day 6. On Days 2 through 5, alvimopan or matching placebo was administered twice daily.

Alvimopan: Following oral administration, plasma alvimopan concentrations peaked at approximately 2 hours postdose and thereafter underwent a biphasic decline. Little or no accumulation was observed after BID dosing. The terminal half-life ranged 10-14 hours. The pharmacokinetics of alvimopan was approximately linear after single or multiple doses of up to 18 mg and no further increase in exposure was found from 18 mg to 24 mg (Table 5).

ADL 08-0011: Study 14CL119 was not well designed for determining the single dose pharmacokinetics of ADL 08-0011. Based on other studies, ADL 08-0011 concentrations peaked at approximately 30 hours postdose. After 4 1/2 days of BID dosing, concentrations of ADL 08-0011 were much higher than those after the first dose but steady state was not reached. The terminal half-life ranged 10-18 hrs. ADL 08-0011 AUC increased less than proportionally with increasing alvimopan doses (Table 6).

Variability: The variability in PK parameters was high for alvimopan (CV for AUC: nearly 60%) and even higher for ADL 08-0011 (CV for AUC: up to >100%) as shown in Tables 5 and 6.

Table 5: Mean alvimopan PK parameters following single- and multiple-dose administrations of alvimopan

Alvimopan Parameter	6 mg	12 mg	18 mg	24 mg
		Single-Dose		
C _{max} (ng/mL) (%CV)	5.07±3.61 (71.2)	12.05±6.74 (55.9)	16.19±4.74 (29.3)	15.88±10.62 (66.9)
T _{max} (hr) (%CV)	1.8±0.7 (37.4)	1.8±0.3 (15.3)	1.8±0.7 (35.9)	1.9±1.3 (66.8)
T _{1/2 z} (hr) (%CV)	3.4±4.2 (122.5)	3.1±1.7 (56.5)	7.5±3.0 (39.2)	7.6±5.9 (78.4)
AUC(0-∞) (hr*ng/mL) (%CV)	20.5±11.5 (56.2)	46.4±22.2 (47.8)	72.4±24.3 (33.6)	62.2±35.4 (56.9)
		Multiple-Dose		
C _{max} (ng/mL) (%CV)	6.41±6.26 (97.6)	10.98±6.43 (58.6)	15.48±9.12 (58.9)	13.85±6.77 (48.9)
T _{max} (hr) (%CV)	1.7±0.6 (35.2)	1.4±0.9 (63.0)	1.4±0.5 (32.8)	1.3±0.4 (29.7)
T _{1/2 z} (hr) (%CV)	7.0±7.6 (108.3)	13.8±7.8 (56.3)	10.1±4.8 (47.3)	12.7±4.8 (38.0)
AUC(0-12) (hr*ng/mL) (%CV)	23.3±13.8 (59.2)	40.2±22.5 (55.9)	62.9±34.5 (54.8)	57.0±29.6 (51.8)
Accumulation Index (%CV)	2.26±3.18 (140.7)	0.98±0.50 (51.0)	1.06±0.54 (50.6)	1.22±0.66 (54.2)

Table 6: Mean ADL 08-0011 PK Parameters following single- and multiple-dose administrations of alvimopan

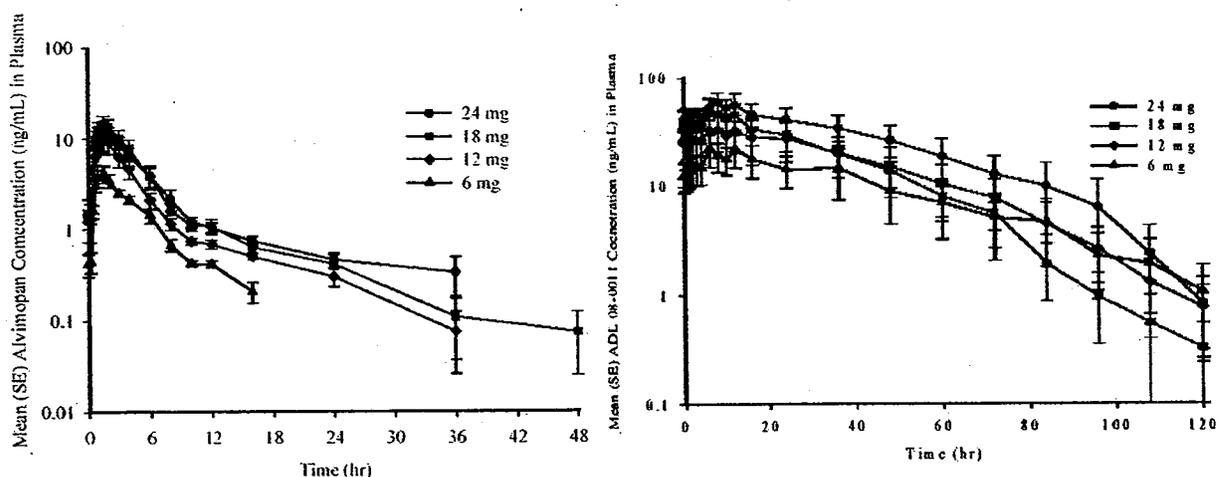
Parameter	6 mg	12 mg	18 mg	24 mg
		Single-Dose		
C _{max} (ng/mL) ^a	6.80 ± 4.75	7.49 ± 6.29	7.83 ± 5.78	19.35 ± 19.74
T _{max} (hr) ^a	20.0 ± 7.41	20.50 ± 6.57	20.25 ± 7.13	17.50 ± 7.31
AUC(0-24) (hr*ng/mL)	81.87 ± 57.29	103.47 ± 94.48	101.40 ± 82.35	264.01 ± 306.08
		Multiple-Dose		
C _{max} (ng/mL) (%CV)	23.61±19.98 (84.6)	35.73±35.29 (98.8)	54.55±40.48 (74.2)	70.39±45.57 (64.7)
T _{max} (hr) ^b (%CV)	8.9±2.8 (31.6)	8.7±4.6 (52.5)	7.8±3.5 (44.3)	7.6±5.0 (65.1)
t _{1/2 z} (hr) (%CV)	18.1±14.7 (81.4)	12.1±5.2 (42.8)	10.6±2.4 (22.9)	10.3±3.4 (32.6)
AUC ^c (hr*ng/mL) (%CV) Geo. mean	422.5±351.2 (83.1) 290.9	706.2±789.4 (111.8) 447.9	929.2±733.5 (78.9) 691.9	1152.5±739.8 (64.2) 950.4

^a An underestimate because the sampling time was too short to cover true C_{max}.

^b The values cannot be interpreted in a conventional way as peak concentrations appeared after 24 h postdose.

^c Because steady state was not reached, the AUC is an underestimate of AUC_{(0-12)ss}.

Fig. 3: Mean Plasma Concentration-Time Profiles After the 9th Dose on Day 6 (Left Panel: Alvimopan; Right Panel: ADL 08-0011)



2.2.8 Does the PK of alvimopan in patients differ from that in healthy volunteers?

Patients on antibiotics: It is postulated that ADL 08-0011 is formed as a result of the degradation of alvimopan by gut microflora. ADL 08-0011 concentrations may be expected to be lower in patients on antibiotics. In the sponsor's population PK analysis, the bioavailability (AUC) of ADL 08-0011 in patients who received pre-surgery antibiotics was approximately 81% lower than that in other subjects. However, the sponsor will be requested to provide further information related to PPK analysis as described in a latter section.

Crohn's patients:

The pharmacokinetics of alvimopan and ADL 08-0011 were determined in patients with active (CDAI >150; N=6) or quiescent Crohn's disease (CDAI ≤150; N=6). All subjects (age: 20-66 yrs; wt: 55-91 kg; 4M & 8 F; all Caucasians) received a single oral dose of alvimopan 12 mg under fasting condition. There were no healthy control subjects in this study for direct comparison.

Mean alvimopan C_{max} and AUC in patients with active Crohn's disease appeared to be similar to those found in healthy subjects in other studies. Patients with quiescent Crohn's disease had higher alvimopan concentrations (~2x) than those with active Crohn's disease (Table 7). ADL 08-0011 C_{max} tended to be lower in patients with Crohn's disease, especially those in quiescent stages when compared to earlier studies in healthy subjects (Table 8). It is noted that the T_{max} for ADL 08-0011 was unusually short (~10 hrs vs. >30 hrs). However, the sampling time of 48 hours was too short for accurate determination of ADL 08-0011 AUC and the infrequent sampling might affect T_{max} and C_{max} determinations as well.

Table 7: Mean Alvimopan PK Parameters Following a Single 12 mg Alvimopan Dose in Patients With Crohn's Disease in the Active and Quiescent Stages

Alvimopan Parameter	Active N = 6	Quiescent N = 6	All patients N = 12
C _{max} (ng/mL) (CV%) Geometric Mean	13.89 ± 11.69 (84.2) 8.92	25.28 ± 15.18 (60.0) 21.95	19.59 ± 14.22 (72.6) 13.99
T _{max} (hr) (CV%)	2.3 ± 0.8 (35.0)	2.2 ± 0.4 (18.8)	2.3 ± 0.6 (27.6)
t _{1/2} (hr) (CV%)	6.7 ± 4.6 (68.9)	2.6 ± 1.8 (69.5)	4.6 ± 3.9 (84.9)
AUC(0-∞) (hr*ng/mL) (CV%) Geometric Mean	52.0 ± 35.5 (68.3) 40.5	94.4 ± 53.1 (56.2) 82.7	73.2 ± 48.4 (66.1) 57.9

Table 8: Mean ADL 08-0011 PK Parameters Following a Single 12 mg Alvimopan Dose in Patients With Crohn's Disease in the Active and Quiescent Stages

ADL 08-0011 Parameter*	Active N = 6	Quiescent N = 6	All Patients N = 12
C _{max} (ng/mL) (CV%) Geometric Mean	3.56 ± 1.89 (53.1) 2.98	2.10 ± 2.19 (104.3) 1.47	2.83 ± 2.09 (74.0) 2.09
T _{max} (hr) (CV%) Geometric Mean	14.3 ± 11.3 (79.0) 7.4	8.5 ± 9.3 (109.5) 3.9	11.4 ± 10.3 (90.6) 5.4
AUC(0-t _{last}) (hr*ng/mL) (CV%) Geometric Mean	106.1 ± 77.4 (72.9) 65.9	79.7 ± 77.8 (97.6) 56.3	94.4 ± 73.9 (78.3) 61.5

* The sampling time of 48 hours was too short for accurate determination of ADL 08-0011 AUC and the infrequent sampling might affect T_{max} and C_{max} determinations as well.

2.2.9 What are the characteristics of drug absorption?

The bioavailability of alvimopan was determined in Study 14CL127. This was an open-label, 3-period crossover study. Thirty-six subjects (24 M/12 F; 18-38 yrs; 51-96 kg; race: 2C/15B/1A) participated in the study. Each subject received under fasted conditions a single 12 mg oral dose (2 x 6 mg capsule; test article), a single 12 mg/50 mL oral solution dose (oral reference), and a single 12 mg i.v. dose (i.v. reference, as a 12 min infusion) during each of the three periods with a minimum 14-day washout.

- The absolute bioavailabilities of alvimopan from oral capsule was 6.0% (95% CI: 4.7-7.7%).
- The bioavailability of alvimopan capsule relative to oral solution was 41.9% (95% CI: 32.6-53.7%).
- Peak plasma alvimopan concentrations occurred at 2 hours postdose for the capsule formulation (and 1 hour postdose for the solution).

Table 9: Mean PK Parameters following oral administration of alvimopan 12 mg in three dosage forms (capsules, oral solution and IV injection)

Route	Dosage Form	Dose (mg)	C _{max} ^a (ng/mL)	T _{max} ^b (h)	t _{1/2} ^a (h)	AUC ^a (ng•h/mL)	CL _p ^a or CL/F (mL/min)	V _{ss} ^a (L)	Comments
p.o.	alvimopan 6 mg Capsule	12 SD	9.49±5.72 (60.2) 7.7	2.0 (1.0, 4.0)	6.2±6.7 (108.5) 3.9	37.4±21.2 (56.6) 30.2	8809±7579 (86.0) 6614	--	F = 6% (95% CI 4.7-7.7)
p.o.	oral solution 12 mg / 50 mL	12 SD	21.81±9.99 (45.8) 20.0	1.0 (0.5, 3.0)	5.5±4.4 (81.0) 4.4	80.7±36.7 (45.5) 73.2	3014±1423 (47.2) 2731	--	F = 14% (95% CI 11.1-18.3)
i.v.	i.v. solution 1 mg/mL (1 mg/min infusion)	12 SD	1017±275 (27.0) 981	0.2 (0.2, 0.25)	5.3±3.8 (72.5) 4.2	522.5±122.4 (23.4) 509.5	402 ± 89 (22.1) 393	30±10 (34.4) 29	

^aAll values of C_{max}, AUC, t_{1/2}, CL (or CL/F) and V_{ss} shown as mean ± sd (CV%), geometric LS mean.

^bValues of T_{max} shown as median (min-max).

SD - single dose; CI - confidence intervals

2.2.10 What are the characteristics of drug distribution?

The (geometric) mean steady state volume of distribution (V_{ss}) was 30±10 L following single IV administration of alvimopan 12 mg.

Alvimopan was not highly bound to human plasma proteins (unbound: 19.5±2.0 %) and binding was concentration-independent over the range of 1 to 100 ng/ml. Binding was mostly to albumin while binding to 0.1% human α₁-acid glycoprotein was negligible (>99% free).

ADL 08-0011 exhibited a higher degree of protein binding in each matrix than the parent compound. The extent of binding was similar in 4% HSA and human plasma (%unbound: 5.9±0.1 and 7.1±0.6%, respectively). Binding of *ADL 08-0011* to 0.1% human α₁-acid glycoprotein was negligible (>90% free). Binding in each matrix was concentration-independent over the range of 10 to 500 ng/ml.

Table 10: Mean±SD %unbound of alvimopan and ADL 08-0011 with various human plasma components

Compound	Conc. (ng/mL)	% Unbound		
		Human Plasma	4% Human Serum Albumin	α ₁ -Acid glycoprotein
Alvimopan	1	21.5 ± 0.4	16.1 ± 0.1	99.9 ± 0.9
	10	17.5 ± 0.4	16.5 ± 0.1	99.3 ± 0.3
	100	19.5 ± 0.2	14.7 ± 0.1	98.8 ± 0.1
ADL 08-0011	10	7.6 ± 0.1	5.8 ± 0.1	92.9 ± 2.2
	100	6.4 ± 0.1	5.9 ± 0.1	92.5 ± 1.8
	500	7.4 ± 0.1	6.0 ± 0.0	91.4 ± 0.5

2.2.11 Is renal or hepatic pathway the major route of alvimopan elimination?

In a mass balance study (Study 14C114), a single oral 12-mg dose of alvimopan containing [¹⁴C] labeled drug (~ 100 Ci) was administered to six normal healthy male subjects (age: 32±8.8 yrs; wt: 82.0±6.2 kg; race: 4C/1B/1H). Urine, feces, and plasma samples were analyzed to determine the metabolic profile of radiolabeled alvimopan.

The mean total recovery of radioactivity in excreta was approximately 83% of the administered dose (feces: 73%; urine: 10%). The primary compound found in the excreta was the parent compound (53.5%) followed by ADL 08-0011 (27.6%). Approximately 2% of the administered dose was excreted unchanged in the urine. Given that the absolute oral bioavailability was approximately 6%, renal clearance is only one third of the total body clearance. The “metabolites” found in this study were the amide hydrolysis compound, ADL 08-0011, and its glucuronide (H7), and an oxidative metabolite (H10).

Although the mass balance study showed a high variability in renal excretion of the parent compound, other studies have consistently shown a renal excretion of 2.2-2.9% of the administered dose up to a dose of 18 mg. Total plasma clearance was estimated to be 402±89 mL/min (Study 14CL127) while renal clearance was estimated to be 100 to 134 mL/min (Study 14CL119). Therefore, renal clearance accounts for approximately 30% of the total plasma clearance. Non-renal pathway is the major route of alvimopan elimination.

Table 11: Mean Recovery of Radioactivity in Feces and Urine

Compound	Mean % of Dose	
	Feces	Urine
Parent (ADL 8-2698)	51.4 ± 16.6	2.1 ± 2.4
Amide Hydrolysis (ADL 08-0011; H3)	21.6 ± 14.3	6.0 ± 4.1
Glucuronide of H3 (H7)	ND	1.4 ± 1.2
Di-oxidative Metabolite (H10)*	ND	0.1 ± 0.2
Total	73.0	9.6

* With a net addition of 30 atomic mass units to ADL 8-2698

2.2.12 What are the characteristics of alvimopan metabolism?

In vitro metabolism studies:

In an *in vitro* study, incubation of alvimopan (0.1, 1 and 10 M) with cryopreserved human hepatocytes pooled from 5 donors did not detect any metabolite. Subsequently, freshly-isolated human hepatocytes (0.7 x 10⁶ cells/mL) from 2 donors and verified with respect to CYP1A2, 2A6 and 2C9 activities were used. Only the oxidative metabolite (H10) was detected at the alvimopan concentration of 1 M or greater. No formation of ADL 08-0011 or its glucuronide was detected.

Formation of ADL 08-0011:

It should be noted that ADL 08-0011 was also present in human plasma following IV administration of alvimopan. Total AUC for ADL 08-0011 following IV administration was approximately half of that observed with oral administration when given at the same dose.

Table 12: ADL 08-0011 PK parameters Following administration of alvimopan 12 mg as oral capsule, oral solution and IV injection

ADL 08-0011 Parameter	Oral Capsule	Oral Solution	I.V. Formulation
C _{max}	6.28 ± 4.57	6.19 ± 4.95	2.88 ± 1.87
(%CV)	(72.7)	(79.9)	(65.0)
Geo. mean	4.72	3.98	2.23
T _{max}	41.2 ± 19.2	36.2 ± 22.3	44.9 ± 24.8
(%CV)	(46.6)	(61.6)	(55.3)
AUC _{0-∞}	358.1 ± 267.9	262.7 ± 111.2	153.9 ± 94.5
(%CV)	(74.8)	(42.3)	(61.4)
Geo. mean	266.8	235.8	126.5
AUC (ADL 08-0011) /AUC (Parent)	13.88 ± 12.29	5.13 ± 4.09	0.29 ± 0.20
(%CV)	(88.5)	(79.7)	(66.9)
Geo. mean	8.43	3.64	0.24

Since ADL 08-0011 was a major compound found in human plasma but was not found in the *in vitro* metabolism study, the sponsor suggests that ADL 08-0011 was formed by GI flora through hydrolysis of the amide functional group in alvimopan. The source of alvimopan in the gut is either the unabsorbed alvimopan (bioavailability ~6%), or absorbed alvimopan that is subsequently secreted into the bile. This may be the reason for the delayed appearance of ADL 08-0011 in the plasma (mean T_{max} > 30 hours). The sponsor has some nonclinical data as listed below that are consistent with this hypothesis. However, there is no hard evidence of biliary secretion of alvimopan in humans.

- a. *Anarobic incubation of alvimopan with stool:* Alvimopan was incubated with autoclaved and non-autoclaved stool samples. Analysis was performed at 0, 24, 48 and 72 hours. ADL 08-0011 was found in both stool samples but its concentrations increased with incubation time only in non-autoclaved stool samples, suggesting that the bacterial flora in the stool can cause the formation of ADL 08-0011.

Table 13: Formation of ADL 08-0011 in autoclaved and un-autoclaved fecal samples spiked with alvimopan following anaerobic incubation

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Time	Alvimopan Concentration, µg/mL			
	72 µg/mL Incubation		144 µg/mL Incubation	
	Autoclaved	Active	Autoclaved	Active
0	71.28 ± 5.85	48.61 ± 10.55	123.4 ± 19.5	58.57 ± 5.29
24	72.22 ± 6.72	48.73 ± 7.27	130.7 ± 23.2	57.37 ± 4.48
48	71.55 ± 4.75	44.07 ± 2.07	118.5 ± 15.4	57.09 ± 6.12
72	72.80 ± 10.14	46.98 ± 7.97	118.2 ± 29.4	55.54 ± 4.67
Group**	71.96 ± 6.90	47.10 ± 7.56	122.7 ± 22.2	57.14 ± 5.10

Time	ADL 08-0011 Concentration, ng/mL			
	72 µg/mL Incubation		144 µg/mL Incubation	
	Autoclaved	Active	Autoclaved	Active
0	66.70 ± 8.58	47.69 ± 15.16	117.5 ± 14.7	84.80 ± 22.64
24	72.38 ± 3.82	104.3 ± 35.0	110.9 ± 10.3	150.5 ± 52.1
48	65.78 ± 5.42	118.4 ± 53.8	102.4 ± 15.0	157.1 ± 38.6
72	64.11 ± 4.94	160.2 ± 118.9	98.43 ± 22.46	205.1 ± 76.3
Group**	67.24 ± 6.54	NC	107.3 ± 17.3	NC

Run Numbers: 021203-891, 021204-802, 021207-803, 021204-804, 021209-845, 021217-806, and 021239-807
 NC: Not calculated. Mean and standard deviation was calculated for concentrations which were constant over time. They were not calculatable for incubations where the concentrations showed an increasing trend with time.
 * Mean and SD were calculated for each timepoint using all of the incubation replicates across all donors, n=10.
 ** As appropriate, group mean and SD were calculated using all of the incubation replicates across all donors and timepoints, n=40.

- b. In Study 7010-103 radiolabeled alvimopan was administered orally or intravenously to bile duct cannulated and un-cannulated dogs. Biliary excretion of total radioactivity accounted for 64.9% of the alvimopan IV dose, suggesting that biliary excretion was extensive. (Reviewer's note: Samples were assayed for radioactivity in this study, and no identification of the compound was made.)

Table 14: Excretion of radioactivity in bile duct cannulated and non-cannulated male dogs

Treatment	Dose Route	Percent of Radioactive Dose			Total
		Urine	Feces	Bile	
Intact bile circulation	Oral	1.14	91.8	NA	93.5
Intact bile circulation	IV	23.5	67.5	NA	92.9
Bile-duct cannulated	Oral	2.34	94.0	6.20	104
Bile-duct cannulated	IV	26.3	1.93	64.9	95.2

*Oral dose: 100 mg/kg; IV dose: 2 mg/kg **Bile: 64.9±2.5% for IV in cannulated dogs

- c. *Evidence of bile secretion of alvimopan in rats:* In rats, biliary excretion of total radioactivity accounted for ~70% of the alvimopan dose following IV administration, and ~5% of the administered dose following oral administration. It was found that the primary compound secreted into the bile was a sulfate conjugate of alvimopan (not seen in human) with <10% of the radioactivity in the bile being alvimopan.

Based on the in vitro metabolism, mass balance and other nonclinical studies, the biotransformation pathway of alvimopan is proposed in Figure 4.

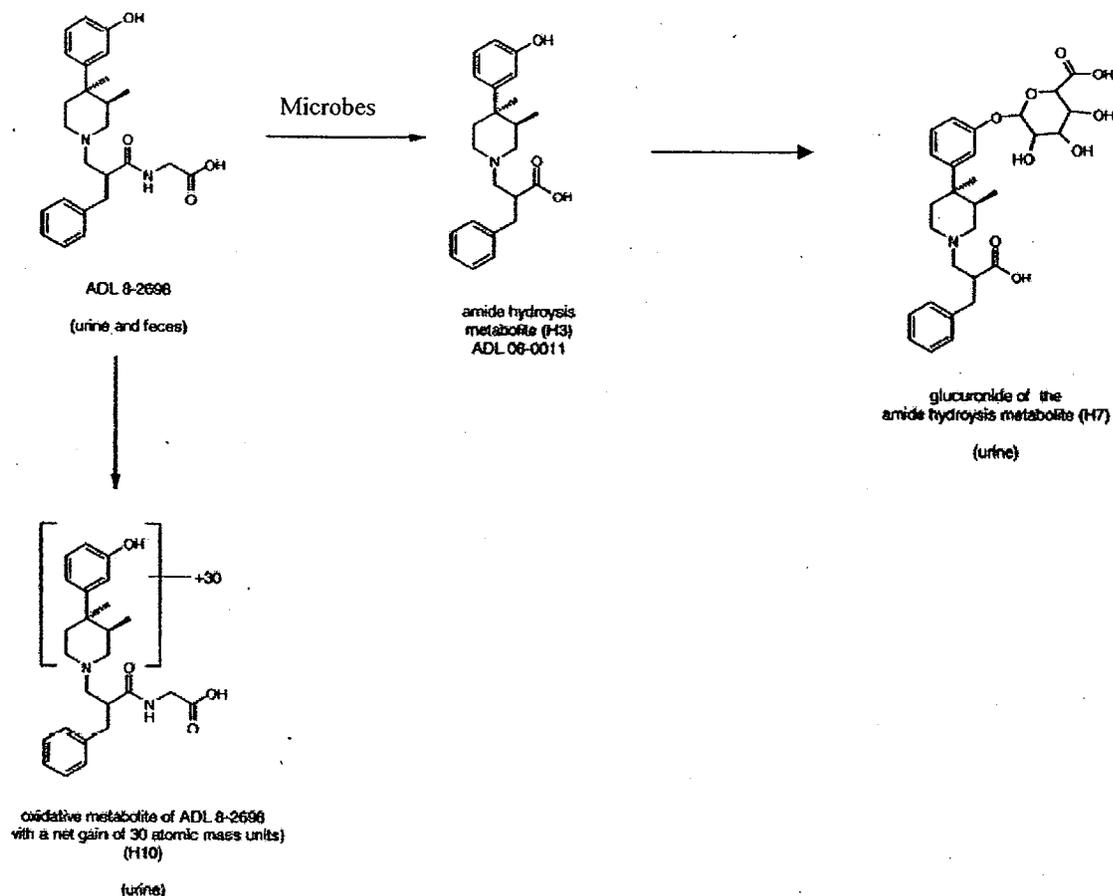


Figure 4: Proposed metabolic pathway of alvimopan in humans

2.2.13 What are the characteristics of alvimopan excretion?

In a mass balance study (Study 14C114), a single oral 12-mg dose of ADL 8-2698 containing [¹⁴C] labeled drug (~ 100 Ci) was administered to six normal healthy male subjects (age: 32±8.8 yrs; wt: 82.0±6.2 kg). Total recovery of radioactivity in urine and feces collected for up to 9 days postdose was approximately 83% (urine: 10%, feces: 73%) of the administered dose. In urine, most of the radioactivity was from ADL 08-0011 (6.0% of the administered dose), followed by alvimopan (2.1% of the dose) and glucuronide of ADL 08-0011 (1.4% of the dose). It is noted that the variability is high. In feces, only alvimopan and ADL 08-0011 were found. Most of the alvimopan in feces was the unabsorbed drug.

Table 15: Mean Recovery of Radioactivity in Feces and Urine

Compound	Mean % of Dose	
	Feces	Urine
Parent (ADL 8-2698)	51.4 ± 16.6	2.1 ± 2.4
Amide Hydrolysis (ADL 08-0011; H3)	21.6 ± 14.3	6.0 ± 4.1
Glucuronide of H3 (H7)	ND	1.4 ± 1.2

Di-oxidative Metabolite (H10)*	ND	0.1 ± 0.2
Total	73.0	9.6

* With a net addition of 30 atomic mass units to ADL 8-2698

2.2.14 Do the pharmacokinetic (PK) parameters for alvimopan and ADL 08-0011 increase proportionally with alvimopan dose?

Bear in mind the high variability in alvimopan pharmacokinetics, the data shown in the table below suggest that alvimopan C_{max} and AUC values are roughly dose proportional up to the 18 mg dose, but no further increase was observed in these parameters with the increase of dose from 18 mg to 24 mg (Study 14CL119; Fig. 5A). For ADL 08-0011, C_{max} appears to be roughly dose proportional but AUC increases less than dose proportionally (Fig. 5B).

Table 16: Mean alvimopan and ADL 08-0011 PK parameters at various alvimopan doses

Parameter	6 mg	12 mg	18 mg	24 mg
<i>Alvimopan: Single dose</i>				
C _{max} (ng/mL)	5.07±3.61	12.05±6.74	16.19±4.74	15.88±10.62
(%CV)	(71.2)	(55.9)	(29.3)	(66.9)
AUC(0-∞) (hr*ng/mL)	20.5±11.5	46.4±22.2	72.4±24.3	62.2±35.4
(%CV)	(56.2)	(47.8)	(33.6)	(56.9)
<i>Alvimopan: Multiple dose</i>				
C _{max} (ng/mL)	6.41±6.26	10.98±6.43	15.48±9.12	13.85±6.77
(%CV)	(97.6)	(58.6)	(58.9)	(48.9)
AUC(0-12) (hr*ng/mL)	23.3±13.8	40.2±22.5	62.9±34.5	57.0±29.6
(%CV)	(59.2)	(55.9)	(54.8)	(51.8)
<i>ADL 08-0011*: Multiple Dose</i>				
C _{max} (ng/mL)	23.61±19.98	35.73±35.29	54.55±40.48	70.39±45.57
(%CV)	(84.6)	(98.8)	(74.2)	(64.7)
AUC _c (hr*ng/mL)	422.5±351.2	706.2±789.4	929.2±733.5	1152.5±739.8
(%CV)	(83.1)	(111.8)	(78.9)	(64.2)

*Single dose data for ADL 08-0011 could not be accurately determined due to study design.

Fig. 5A: Dose normalized alvimopan PK parameters vs. Alvimopan Dose
(Single dose parameters: C_{max,s} and AUC_s
Multiple dose parameters: C_{max,m} and AUC_m)

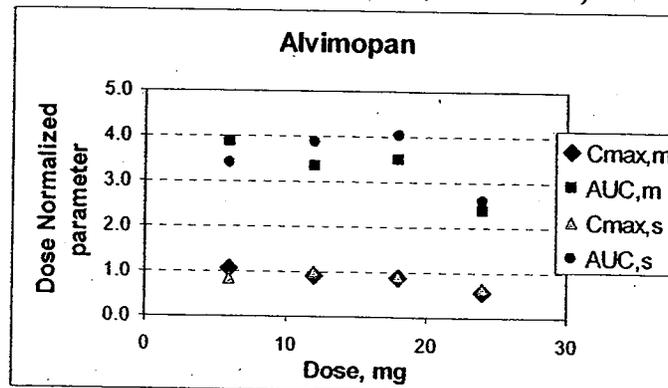
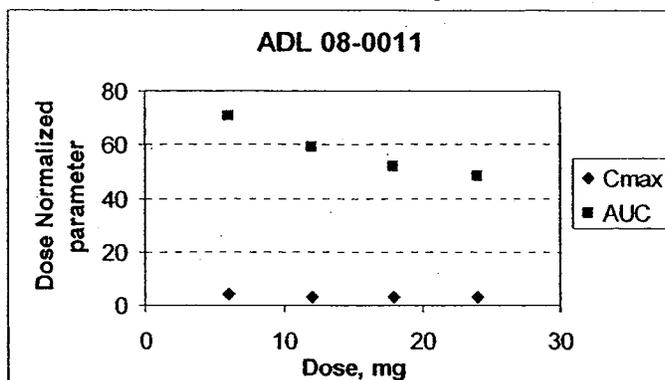


Fig. 5B: Dose normalized ADL 08-0011 PK parameters vs. Alvimopan Dose



2.2.15 Is there accumulation in alvimopan and ADL 08-0011 concentrations following multiple dosing of alvimopan?

No evidence of accumulation in alvimopan concentration was observed after 6 days of BID dosing. Accumulation of ADL 08-0011 upon BID dosing is expected based on its PK characteristics. However, the accumulation ratio could not be determined in Study 14CL119 due to the study design (i.e., the single dose phase was not characterized long enough to obtain a full profile).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure or response to alvimopan? What is the impact of these factors on exposure and response?

Several studies were performed in special populations. However, most studies were not well designed to be self-sufficient. Two population PK analyses were conducted to investigate the impact of intrinsic factors. The first analysis included one Phase 3 trial in which one sample per patient was collected. These were considered to be weak data. The second analysis included one more Phase 3 trial in which 7 samples per patients were collected. Therefore, the second analysis is the basis for the discussions in this review.

A conventional 2-compartment model with a lag time in absorption was used to describe alvimopan PK. For ADL 08-0011, a 1-compartment model with a time lag and a catenary chain to explain the transport of alvimopan to the site of metabolism as well as its metabolism and systemic absorption.

The following comments pertain to the population PK analysis:

- Some covariates were found to impact on the fraction of drug absorbed (F). It is unclear whether the covariates were tested for their impact on CL (or CL/F).
- In the population PK dataset, creatinine clearance (CL_{cr}) ranged up to >300 mL/min. In the calculation of CL_{cr}, adjustment may be made for subjects with high BMI. Alternatively, a

maximum limit in CL_{cr} may be imposed in the population PK analysis. This, however, does not seem to have been done based on the control codes provided.

- V_{ss}/F was estimated to be 1949 L from the population PK analysis, which is much higher than expected from a V_{ss} estimate of 30 L following IV administration and a F of <10%. The model does not seem to describe well the alvimopan pharmacokinetics.
- For analysis pertaining to drug-drug interactions, separate analysis should be performed for each drug. In addition, a table should be provided listing the number of patients on each dose.
- It is noted that some covariates are concentrated in certain studies. For the information to be included in the label, covariates should be further examined/tested to verify that samples size was adequate and that the impact of the covariate was not driven by one particular study.
- The population PK analysis will be reviewed in detail when the above issues are addressed.
- The sponsor's population PK results for each covariate are described in the section below without reiterating the above comments.

A. Age

A single-dose study (Study 14CL123) was conducted in 18 elderly subjects (9 males: 77 ± 9.5 kg and 9 females: 65±8.6 kg; age: 73 ± 4.6 yrs; race: 16C/1A/1H). Since there were no young subjects in the study, the parameters were tabulated along with data from other studies in young healthy volunteers (see Table below). Age effect on alvimopan and ADL 08-0011 PK is not apparent based on the information listed in Table 17.

The population PK analysis indicated that bioavailability decreased by 0.7% per year in age.

Table 17: PK parameters (elderly vs. young) following single dose administration of alvimopan 12 mg

Parameter	Alvimopan			ADL 08-0011		
	Elderly (Study 123)	Young (Study127)	Young (Study124)	Elderly (Study 123)	Young (Study127)	Young (Study124)
C _{max} (ng/mL)	10.37 ± 4.39 (42.3%)	9.49 ± 5.72 (60.2%)	11.96±6.32 (52.9%)	6.15 ± 4.33 (70.4%)	6.28±4.57 (72.7%)	6.6 ± 3.8 (57.8%)
Geo.Mean	9.57	7.7	10.21	4.56	4.72	5.33
AUC(0-∞), (hr*ng/mL)	41.7 ± 19.9 (47.7%)	37.4 ± 21.2 (56.6%)	53.1 ± 27.8 (52.3%)	285.5 ± 188.6 (66.1%)	358.1±267.9 (74.8%)	-
Geo. Mean	38.1	30.2	46.6	201.0	266.8	-
t _{1/2 λ z} (hr)	5.1 ± 2.6 (50.9%)	-	5.3 ± 5.4	24.8 ± 19.4 (78.1%)	-	-

*The value might be an underestimate of AUC_∞ because of short sampling time of 96 hrs.

B. Gender

There is no prospectively designed study to look at gender effect. An examination of Study 14CL123 (9 elderly males & 9 elderly females) indicated that alvimopan CL/F values in six females covered the same range as that in the nine males, with the other three females having higher CL/F values. In the population PK analysis, gender was not detected as a factor affecting alvimopan or ADL 08-0011 pharmacokinetics.

C. Race

Race was examined in the population PK analysis. Bioavailability of ADL 08-0011 was 82% lower in Hispanics and 43% lower in African-Americans than that in Caucasians.

D. Renal Impairment

In Study 14CL116, 24 subjects with various degrees of renal function were enrolled with 6 subjects in each of the four groups based upon their degree of renal impairment (healthy, mild, moderate, or severe). All subjects received a single 12 mg oral dose of alvimopan. Dose administration occurred after a minimum 6-hour fast (nothing by mouth) and was to be followed by a fast from food (not including water) for at least 4 hours post-dose. Blood samples were collected for up to 120 hours postdose and urine samples were collected for up to 24 hours postdose.

Alvimopan: There was no relationship between renal function (i.e., creatinine clearance) and plasma alvimopan pharmacokinetics (Fig. 6A and Table 18). The mean alvimopan renal clearances decreased with decreasing renal function.

ADL 08-0011: On the other hand, ADL 08-0011 concentrations were higher in the moderate (AUC: ↑54%) to severe (AUC: ↑309%) renal impairment patients (Fig. 6B and Table 19). The plasma AUC ratio (metabolite AUC/parent AUC) was about 5 for the control group and about 2, 8, and 15 for the mild, moderate, and severe renal groups, respectively. High variability in alvimopan and ADL 08-0011 PK parameters was observed.

Population PK: The population PK analysis did not detect renal function as a factor influencing alvimopan or ADL 08-0011 pharmacokinetics. However, there appears to be weakness in the analysis as stated above.

Figure 6A: Mean Alvimopan Concentrations (ng/mL) in Plasma Following a Single 12 mg Dose to Subjects with Various Degrees of Renal Impairment

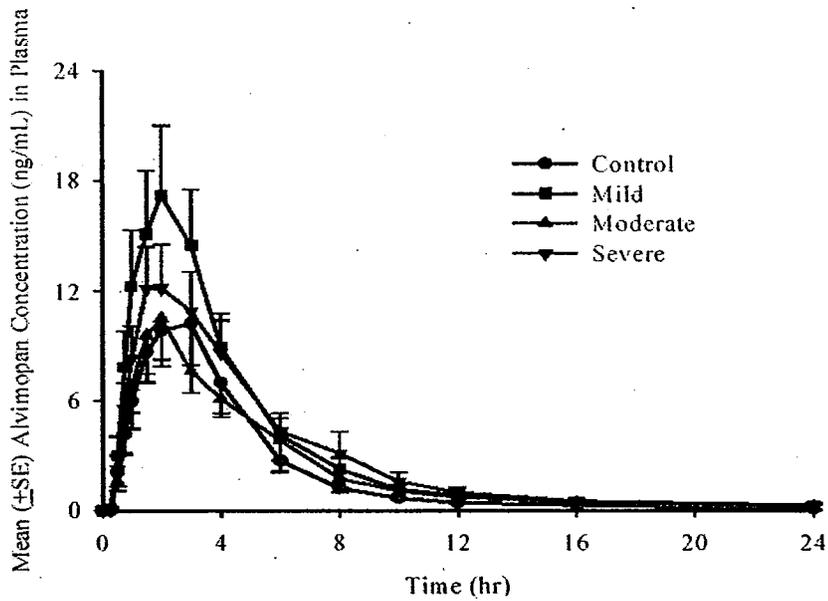


Figure 6B: Mean (±SE) ADL 08-0011 Concentrations (ng/mL) in Plasma Following a Single 12 mg Dose to Subjects with Various Degrees of Renal Impairment

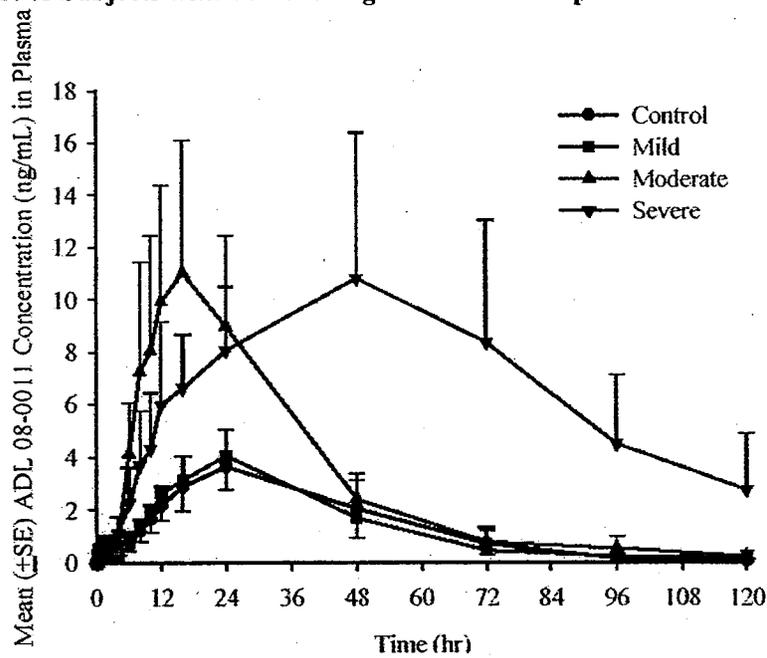


Table 18: Mean Alvimopan PK parameters in patients with various degree of renal impairment

Alvimopan Parameter	Renal Impairment Classification			
	Mild (N=6)	Moderate (N=6)	Severe (N=6)	Normals (N=6)
C _{max} (ng/mL)	17.93 ± 9.42	11.71 ± 4.93	13.39 ± 5.38	12.15 ± 4.49
(%CV)	(52.5)	(42.1)	(40.2)	(36.9)

Geometric mean	15.65	10.78	11.84	11.34
Tmax (hr)	2.0±0.6	2.3±1.1	2.0±0.5	2.1±0.7
(%CV)	(31.6)	(48.2)	(27.4)	(35.3)
T½z (hr)	5.16±2.41	5.45±3.97	9.57±6.89	5.65±3.03
(%CV)	(46.8)	(72.9)	(72.0)	(53.5)
AUC(0-∞) (hr*ng/mL)	78.6±40.1	53.1±22.5	74.9±38.3	49.8±19.1
(%CV)	(51.0)	(42.4)	(51.1)	(38.4)
Geometric mean	69.1	49.9	62.2	46.1
CLr (mL/min)	26.4±22.3	12.7±13.3	5.1±4.2	38.4±19.0
(%CV)	(84.7%)	(105.2)	(81.4)	(49.6)

Table 19: Mean ADL 08-0011 PK parameters in patients with various degree of renal impairment

ADL 08-0011 Parameter	Renal Impairment Classification			
	Mild (N=6)	Moderate (N=6)	Severe (N=6)	Normals (N=6)
Cmax (ng/mL)	4.96±2.99	11.60±9.96	15.27±12.20	3.89±3.70
(%CV)	(60.3)	(85.9)	(79.9)	(95.1)
Geometric mean	4.29	7.38	10.29	2.50
Tmax (hr)	26.0±11.8	14.3±8.4	36.7±23.2	32.0±12.4
(%CV)	(45.4)	(58.8)	(63.4)	(35.3)
T½z (hr)	25.58±17.99	24.30±20.38	27.79±27.70	16.04±1.73
(%CV)	(70.3)	(83.9)	(99.7)	(10.8)
AUC(0-∞) (hr*ng/mL)	174.1±84.6	409.4±323.2	1089.9±1280.8	266.7±242.9
(%CV)	(48.6)	(79.0)	(117.5)	(91.1)
Geometric mean	154.3	281.3	508.3	161.7

E. Hepatic Insufficiency

In Study 14CL117, 16 subjects with hepatic impairment (mild or moderate as determined by Child-Pugh Scores) were enrolled. In addition, each hepatic impairment group was matched with two normal subjects whose mean age and weight were within 10% of those for the hepatically impaired subjects. All subjects received a single 12 mg oral dose of alvimopan. (The number of healthy subjects is only 4 after pooling.)

Alvimopan and ADL 08-0011: Although there is a trend towards higher exposure (AUC) in mild to moderate hepatic impairment patients, there is also a high degree of overlapping with healthy subjects as shown in Figure 7. The number of subjects is small, especially in view of the high variability. (Note: This study was not well balanced with respect to body weight and race across various hepatic impairment groups. The alvimopan exposure parameters in healthy subjects participating in this study were only approximately half of those observed in other studies.)

Data from this hepatic impairment study was not included in the population PK analysis.

Table 20:

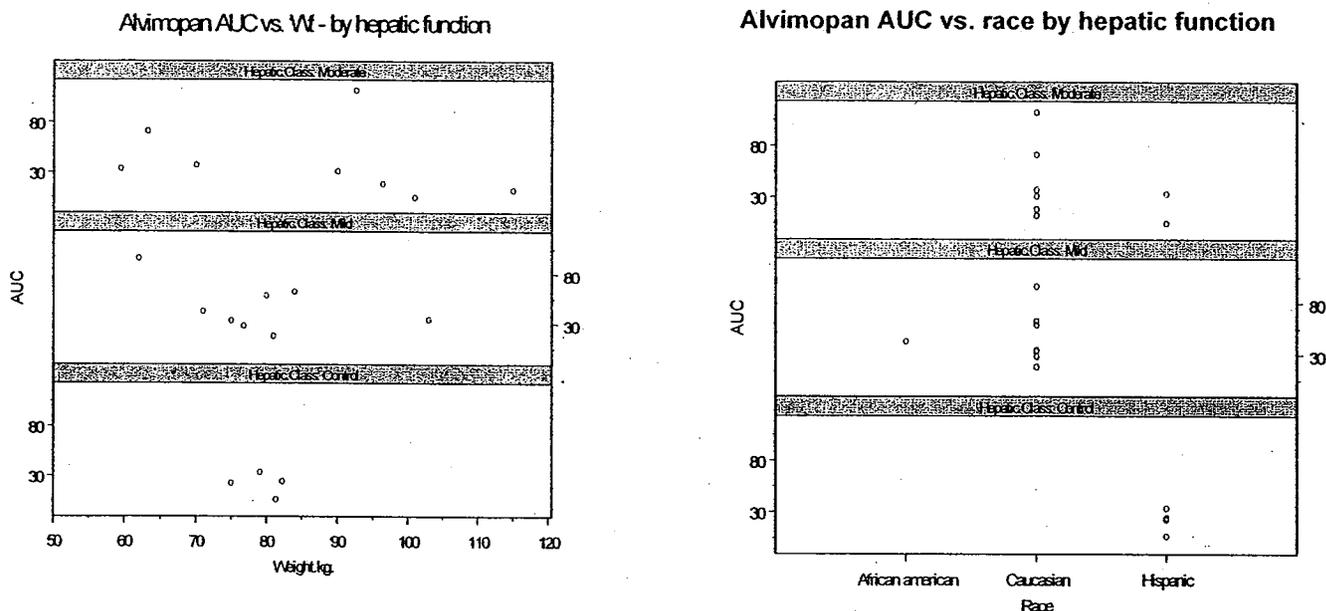
Summary of Pharmacokinetic Parameters of Alvimopan After a Single 12 mg Alvimopan Dose			
Parameter	Hepatic Impairment Status		
	Mild (N=8)	Moderate (N=8)	Matched Normals (N=4)
C_{max} (ng/mL)			
Mean ±SD (%CV)	12.64 ± 7.63 (60.4)	7.75 ± 7.82 (100.8)	6.70 ± 4.36 (65.1)
Geometric mean	11.08	4.82	5.03
T_{max} (hr)			
Mean ±SD (%CV)	1.8 ± 1.1 (59.3)	1.5 ± 0.7 (47.1)	1.8 ± 1.0 (54.7)
Geometric mean	1.6	1.4	1.6
Median (Range)	1.5 (0.8-4.0)	1.25 (1.0-3.0)	1.5 (1.0-3.0)
t_{1/2z} (hr)			
Mean ±SD (%CV)	6.83 ± 4.82 (70.6)	15.40 ± 21.58 (140.1)	7.14 ± 5.66 (79.3)
Geometric mean	5.49	7.93	5.55
AUC(0-∞) (hr*ng/mL)			
Mean ±SD (%CV)	46.5 ± 24.9 (53.6)	39.9 ± 35.5 (88.9)	21.9 ± 11.3 (51.8)
Geometric mean	41.2	27.4	18.7

Table 21:
Summary of Pharmacokinetic Parameters of ADL 08-0011 After a Single 12 mg Alvimopan Dose

Parameter	Hepatic Impairment Status		
	Mild N=8	Moderate N=8	Matched Normals N=4
C_{max} (ng/mL)			
Mean ±SD (%CV)	6.65 ± 7.36 (110.6)	3.38 ± 2.98 (88.3)	2.71 ± 1.25 (46.2)
Geometric mean	3.78	2.35	2.41
T_{max} (hr)			
Mean ±SD (%CV)	25.1 ± 23.7 (94.6)	17.4 ± 23.4 (134.9)	13.0 ± 7.7 (59.6)
Geometric mean	14.3	6.7	11.5
Median (Range)	18.0 (0.8-72.0)	10.0 (0.5-72.0)	11.0 (6.0-24.0)
t_{1/2z} (hr)			
Mean ±SD (%CV)	23.3 ± 9.2 (39.6)	12.1 ± 8.7 (72.1)	10.6 ± 7.1 (67.0)
Geometric mean	21.7	9.9	9.1
AUC(0-last) (hr*ng/mL)			
Mean ±SD (%CV)	315.5 ± 554.7 (175.8)	107.5 ± 142.4 (132.5)	40.5 ± 21.5 (53.1)
Geometric mean	118.6	32.6	36.8
AUC(0-∞) (hr*ng/mL)			
Mean ±SD (%CV)	368.5 ± 663.3 (171.8)	130.8 ± 154.2 (117.9)	34.3 ± 9.6 (28.1)
Geometric mean	136.0	44.2	33.5

Fig. 7: Alvimopan and ADL 08-0011 Exposure in subjects with various degrees of hepatic impairment

Fig. 8: Weight and race distribution by degree of hepatic impairment



In a study in 3 severe hepatic impairment patients with two matching healthy subjects, two patients had alvimopan concentrations similar to the healthy control subjects, while one patient had much higher alvimopan concentrations (Cmax: ~8x, and AUC: ~10x). All three severe hepatic impairment patients had negligible ADL 08-0011 concentrations.

2.3.2 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women. The label states that the drug should be administered during pregnancy only if clearly needed. It also states that alvimopan and ADL 08-0011 are detected in the milk of lactating rats and that caution should be exercised when the drug is administered to a nursing woman.

2.3.3 What are the special considerations for dosing in special populations?

When there are significant changes in alvimopan and/or ADL 08-0011 PK in special populations, the following points need to be considered when making dosing recommendations:

- (1) If the drug activity is derived from local action: According to Dr. Tamal Chakroborti, Pharmacologist of HFD-180, alvimopan (or ADL 08-0011) does not have to be absorbed to exert its action since α -receptors are distributed throughout the GI tract. If this is the case, the drug concentration in the GI tract would be important and what happens to the plasma concentration may not reflect the efficacy. Dosage reduction for patients with higher plasma concentrations can be detrimental to efficacy, especially when the drug is considered relatively safe. (According to Dr. Chakroborti, the NOAEL AUC_{0-24h} was 1800 ng.h/mL in dogs in a one-month study. According to Dr. Eric Brodsky, Medical Officer of HFD-180, the clinical trial did not

show a particular safety concern.) In case of lower plasma concentrations, efficacy is not affected and there is no need to increase the dose.

(2) If the drug works through both local and systemic actions: The relative contribution by either route cannot be quantified. Additionally, the relative contribution by either the parent or ADL 08-0011 is also unknown. The situation is further complicated when parent concentrations are increased but not the ADL 08-0011 concentrations or vice versa. As such, PK is useful in identifying the subpopulation for special considerations. However, clinical findings will be the primary basis for dosage adjustment.

Dosing recommendations for special populations will be considered when efficacy of the drug product is demonstrated.

2.4 Extrinsic Factors

Drug-Drug Interactions

2.4.1 Is there any basis to suspect in vivo drug-drug interactions?

The sponsor postulates that following oral administration of alvimopan, the drug can be degraded by gut microflora to form ADL 08-0011. The drug present in the gut may be the unabsorbed drug or absorbed drug subsequently secreted into the bile. This hypothesis suggests that use of antibiotics may reduce the formation of ADL 08-0011 due to a reduction in gut microflora.

Since both alvimopan and ADL 08-0011 appear to be P-gp substrates, coadministration of alvimopan with P-gp inhibitors may increase the exposure of alvimopan and ADL 08-0011.

2.4.2 Is alvimopan or ADL 08-0011 a substrate of CYP enzyme(s)?

Based on the information provided so far, there is no evidence that alvimopan or ADL 08-0011 is a substrate of CYP enzymes.

2.4.3 Is alvimopan or ADL 08-0011 an inhibitor of CYP enzymes?

No, neither alvimopan nor ADL 08-0011 is likely to be an inhibitor of CYP enzymes.

Inhibition: CYP450 inhibition of alvimopan and ADL 08-0011 at the concentration range of 0, 0.05, 0.165, 0.5, 1.65, 5, 16.5 and 50 μ M were investigated in human liver microsomes (pooled from 16 donors). The mixture of an appropriate probe substrate, human liver microsomes and an NADPH regenerating system was incubated over a known time course at 37°C. The production of metabolite in each incubation was quantified by LC/MS/MS and IC₅₀ values for the inhibition of each enzyme activity were determined. The viability of the system was verified using positive controls for each CYP enzyme investigated. The results indicated that alvimopan and ADL 08-0011 are not likely to be inhibitors of CYP enzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) as evidenced by the high IC₅₀ values. (Note: 50 μ M is equivalent to 23 μ g/mL for alvimopan.)

Table 22: Inhibition of cytochrome P450 activities with Alvimopan (or SB-767905-KW)

P450	Substrate	SB-767905-KW IC50 value (µM)	Positive Control	Positive Control IC50 value (µM)
1A2	Phenacetin	>50	Fluvoxamine	0.054
2A6	Coumarin	>50	Tranylcypromine	0.041
2B6	Bupropion	>50	Orphenadrine	136
2C8	Paclitaxel	>50	Quercetin	2.2
2C9	Diclofenac	>50	Sulphaphenazole	1.4
2C19	S-Mephenytoin	>50	Ticlopidine	0.77
2D6	Bufuralol	>50	Quinidine	0.048
2E1	Chlorzoxazone	>50	4- methyl pyrazole	0.51
3A4	Atorvastatin	>50	Ketoconazole	0.046
3A4	Midazolam	>50	Ketoconazole	0.027
3A4	Nifedipine	>50	Ketoconazole	0.023

Table 23: Inhibition of cytochrome P450 activities with ADL 08-0011 (or SB-791399-GS)

P450	Substrate	SB-791399-GS IC50 value (µM)	Positive Control	Positive Control IC50 value (µM)
1A2	Phenacetin	>50	Fluvoxamine	0.054
2A6	Coumarin	>50	Tranylcypromine	0.041
2B6	Bupropion	>50	Orphenadrine	136
2C8	Paclitaxel	>50	Quercetin	2.2
2C9	Diclofenac	>50	Sulphaphenazole	1.4
2C19	S-Mephenytoin	>50	Ticlopidine	0.77
2D6	Bufuralol	>50	Quinidine	0.048
2E1	Chlorzoxazone	>50	4- methyl pyrazole	0.51
3A4	Atorvastatin	>50	Ketoconazole	0.046
3A4	Midazolam	>50	Ketoconazole	0.027
3A4	Nifedipine	>50	Ketoconazole	0.023

2.4.4 Is alvimopan or ADL 08-0011 an inducer of CYP enzymes?

The sponsor did not conduct any study to investigate the potential of ADL 08-0011 as an inducer of CYP enzymes.

Two studies were conducted to investigate the induction potential of alvimopan at the tested concentrations of 1, 10, and 50 nM. The first study used fresh human hepatocytes from one donor. CYP1A2 activity was characterized by ethoxyresorufin O-deethylation (EROD) with omeprazole as the positive control. CYP3A4 activity was characterized by testosterone 6β-hydroxylation with rifampin as the positive control. The results indicated that alvimopan did not induce CYP3A4 activity, but induced CYP1A2 activity although it was less than the positive control and did not increase with alvimopan concentration.

Table 24: Formation of 6 β -hydroxytestosterone

Sample Number	Control/Test Article	Concentration μ M	6 β -Hydroxytestosterone Formation		Percent of VC
			μ M	pmol/million cells/min	
1	VC	N/A	0.352	8.79	
2			0.385	9.63	
3			0.407	10.2	
4			0.419	10.5	
5			0.408	10.2	
6			0.324	8.08	
Mean \pm SD			9.57 \pm 0.95		100
7	Rifampin	25	2.062	51.7	
8			4.279	107	
9			2.714	67.9	
10			3.073	76.7	
11			3.228	80.8	
12			3.211	80.4	
Mean \pm SD			77.4 ^s \pm 18.2		809
13	Omeprazole	50	0.00*	0.00	
14			0.00*	0.00	
15			0.00*	0.00	
16			0.00*	0.00	
17			0.00*	0.00	
18			0.00*	0.00	
Mean \pm SD			N/A		N/A
19	ADL 8-2698	1	0.376	9.42	
20			0.309	7.71	
21			0.285	7.13	
Mean \pm SD			8.09 \pm 1.19		84.5
22	ADL 8-2698	10	0.282	7.04	
23			0.243	6.08	
24			0.299	7.46	
Mean \pm SD			6.86 \pm 0.71		71.7
25	ADL 8-2698	50	0.196	4.92	
26			0.289	7.21	
27			0.304	7.58	
Mean \pm SD			6.57 \pm 1.44		68.7

The second study investigated the effect of alvimopan on the expression of CYP1A2 activity and mRNA levels in two preparations of cryopreserved cultured human hepatocytes with β -naphthoflavone as the positive control. Microsomal samples were used to measure 7-ethoxyresorufin O-dealkylase (EROD) activity (CYP1A2) and cell lysates were used to measure CYP1A2 mRNA expression by bDNA analysis. The results indicated that β -naphthoflavone caused a 11- and 8.9-fold increase in EROD activity and a 15- and 98-fold increase in CYP1A2 mRNA expression versus vehicle control (0.1% DMSO, v/v). Treatment of cryopreserved cultured human hepatocytes with alvimopan daily for three days did not increase EROD activity or CYP1A2 mRNA levels.

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Table 25: Rate of ethoxyresorufin O-dealkylation and mRNA expression

Treatment	Concentration	7-Ethoxyresorufin O-dealkylation (pmol/mg protein/min) ^{a,b}	CYP1A2 mRNA Expression (% GAPDH) ^{a,c}
DMSO	0.1% (v/v)	2.85/3.80 (1.0/1.0)	12.1/0.630 (1.0/1.0)
Alvimopan	1 μM	3.12/3.38 (1.1/0.89)	6.22/1.31 (0.51/2.1)
Alvimopan	10 μM	2.53/4.09 (0.89/1.1)	10.5/0.77 (0.86/1.2)
Alvimopan	50 μM	2.50/3.09 (0.88/0.81)	6.79/1.72 (0.56/2.7)
β-Naphthoflavone	33 μM	31.4/31.9 (11/8.4)	187/62.1 (15/98)

DMSO: Dimethyl sulfoxide

GAPDH: glyceraldehyde 3-phosphate dehydrogenase

^a Values are the rates for two of human hepatocyte preparations (H382 and H393, respectively), rounded to three significant figures.

^b Values are the fold increase over vehicle control (0.1% DMSO) for two human hepatocyte preparations (H382 and H393, respectively), rounded to two significant figures.

^c Values are the fold increase over vehicle control (0.1% DMSO) for two human hepatocyte preparations (H382 and H393, respectively), rounded to two significant figures; Fold increase = % GAPDH / % of GAPDH of 0.1% DMSO of appropriate human.

Because conflicting results were obtained in the two studies for CYP1A2 induction by alvimopan and no studies were conducted with ADL 08-0011, we recommend that the sponsor conduct *in vitro* studies to investigate the potential for alvimopan and ADL 08-0011 as inducers of CYP enzymes. Hepatocytes from at least 3 human donors should be tested.

2.4.5 Is alvimopan or ADL 08-0011 a substrate of P-glycoprotein (P-gp) transporter processes?

Caco-2 cells were used to investigate whether alvimopan or ADL 08-0011 is a P-gp substrate. The permeability buffer was Hank's Balanced Salt Solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.0±0.2. Alternatively assay buffer also contained 2μM of P-gp inhibitor, GF120918, on both the apical and basolateral sides. GF120918 had no effect on the passively permeating control compounds (atenolol and propranolol), but completely inhibited secretory transport of digoxin.

Table 26

.2 Certification	Without inhibitor	With inhibitor	Acceptance Criteria
TEER Value (Ω·cm ²):	589	614	450-650 Ω·cm ²
Lucifer Yellow, Papp x 10 ⁻⁶ cm/s:	0.15	0.22	< 0.4 x 10 ⁻⁶ cm/s
Atenolol, Papp x 10 ⁻⁶ cm/s:	0.14	0.28	< 0.5 x 10 ⁻⁶ cm/s
Propranolol, Papp x 10 ⁻⁶ cm/s:	17	15	15-25 x 10 ⁻⁶ cm/s
Digoxin(A-B), Papp x 10 ⁻⁶ cm/s:	1.7	4.8	none
Digoxin(B-A), Papp x 10 ⁻⁶ cm/s:	16	4.5	none

The study suggested that both alvimopan and ADL 08-0011 were P-gp substrates. ADL 08-0011 showed high permeability based on comparison to reference compounds (atenolol and propranolol). Efflux was completely inhibited by GF120918. Alvimopan has an efflux ratio of 2.9 using buffer alone, and showed no change in A-to-B flux and a small decrease in B-to-A flux in the presence of GF120918.

Table 27
Recovery and Permeability (10^{-6} cm/s) of Test Compounds

Compound Identification	Percent Recovery ^(*)			Papp ^(m) Blank	Papp, A-to-B			Papp, B-to-A			Papp ^{A-B} / Papp ^{B-A} Ratio ^(m)	Absorption Potential ^(m)	Significant Efflux ^(m)
	Blank	A-to-B	B-to-A		Rep. 1	Rep. 2	Avg	Rep. 1	Rep. 2	Avg			
ADL08-0011	86	65	108	31.7	1.97	1.96	1.97	13.2	12.0	12.6	6.4	High	Yes
ADL08-0011 + 2 μ M GF120918	89	92	102	31.9	3.70	3.70	3.70	3.60	3.63	3.61	1.0	High	No
alvimopan	98	94	95	31.8	0.27	0.25	0.26	0.74	0.76	0.75	2.9	Low	No
alvimopan + 2 μ M GF120918	91	92	70	30.8	0.28	0.28	0.28	0.32	0.30	0.31	1.1	Low	No

Absorption Potential Classification:

Papp (A-to-B) $\geq 1.0 \times 10^{-6}$ cm/s

Papp (A-to-B) $> 0.5 \times 10^{-6}$ cm/s, Papp $< 1.0 \times 10^{-6}$ cm/s

Papp (A-to-B) $< 0.5 \times 10^{-6}$ cm/s

High

Medium

Low

2.4.6 Is alvimopan or ADL 08-0011 an inhibitor of P-glycoprotein transporter processes?

The effect of alvimopan or ADL 08-0011 on the P-glycoprotein mediated transport of digoxin (ca. 30 nM) was assessed by determining the basolateral to apical (B→A) transport of [³H]-digoxin by _____ cells in the absence or presence of either test compound at target concentrations of 0.1, 0.3, 1, 3, 10, 30 and 100 μ M (applied in both the apical and basolateral wells). As a positive control, and to determine the passive transport rate of digoxin, GF120918A (an inhibitor of P-glycoprotein) was also investigated at a nominal concentration of 2 μ M. The concentrations of [³H]-digoxin in the donor and receiver wells were determined by scintillation counting. Monolayer integrity at the end of the study was assessed by measuring the passive permeability of the paracellular permeability marker, lucifer yellow. The results indicated that neither alvimopan nor ADL 08-0011 is an in vitro inhibitor of digoxin transport via human P-gp at concentrations up to 100 μ M

Table 28: Inhibition of Human P-gp Transport of Digoxin by Alvimopan (SB-767905)

Treatment	Transport Rate (pmoles/cm ² /h \pm SD)	Transport Rate (% control)	Mass Balance (%)
Digoxin only	1.97 \pm 0.09	100	84
Digoxin + 2 μ M GF120918A	0.35 \pm 0.02	18	83
Digoxin + 0.1 μ M SB-767905	1.90 \pm 0.06	96	84
Digoxin + 0.3 μ M SB-767905	1.83 \pm 0.13	93	85
Digoxin + 1 μ M SB-767905	1.74 \pm 0.03	88	86
Digoxin + 3 μ M SB-767905	1.89 \pm 0.15	96	81
Digoxin + 10 μ M SB-767905 *	1.69, 1.86	86, 94	82, 85
Digoxin + 30 μ M SB-767905	2.04 \pm 0.07	103	82
Digoxin + 100 μ M SB-767905 *	2.02, 2.10	102, 107	91, 87

Data are the average of values obtained from three wells, unless otherwise indicated.

* n=2 as monolayer integrity was not demonstrated in all 3 wells.

** Cell line: polarized Madine-Darby canine kidney _____ cell line _____

2.4.7 Are there other metabolic/transporter pathways that may be important?

No data are available indicating that other metabolic/transporter pathways may be important for alvimopan.

2.4.8 Does the product's label specify co-administration of another drug, and, if so, has the interaction potential between these drugs been evaluated?

The proposed drug product is intended for postoperative ileus. Since opioids are almost universally used for the treatment of acute surgical pain, the sponsor conducted a study to evaluate the effect of alvimopan administration on PK of morphine sulfate IV (MS; 0.05 mg/kg). This was a single-blind, placebo-controlled, crossover study in 10 healthy volunteers (wt: 50.9-96.4 kg; race: 7C/1B/2H; 8M & 2F; age: 38.9±15.8 yrs). Subjects were randomly assigned to one of two treatment sequences:

A: alvimopan 12 mg + MS → alvimopan 12 mg bid (4.5 days) + MS → placebo + MS

B: placebo + MS → alvimopan 12 mg + MS → alvimopan 12 mg bid (4.5 days) + MS

Note: Morphine sulfate IV was given 2 hrs after alvimopan or placebo dose. There was a 4-day washout between placebo and alvimopan phases.

There was a decrease in mean morphine C_{max} (↓66%) and AUC (↓17%) when morphine sulfate IV was administered 2 hours after alvimopan. On the other hand, there was a slight increase in the 6-morphine-glucuronide concentrations (mean C_{max}: ↑4.8%; mean AUC: ↑15.9%) following multiple dosing of alvimopan. It is noted, however, that the variability in these parameters for the placebo phase was significantly higher compared to the alvimopan phase. An inspection of the data indicated that morphine plasma concentration undergoes a biphasic decline (Fig. 8). The overall estimation of the area could be much influenced by the first trapezoidal area or by the accuracy of the sampling time for the first samples. Therefore, there is a possibility that the differences in PK parameters are not real. According to Dr. Eric Brodsky, Medical Officer of HFD-180, morphine doses in surgery patients participated in Phase 3 trials did not appear to creep up in patients who received alvimopan, indicating that administration of alvimopan did not have clinically significant effect on the analgesic effect of morphine. It is concluded that no dosage adjustment for morphine is necessary when it is coadministered with alvimopan.

Figure 7: Mean (±SE) Morphine Concentrations (ng/mL) After a 0.05 mg/kg IV Dose of Morphine Sulfate Given 2 Hours After an Alvimopan or Placebo Dose

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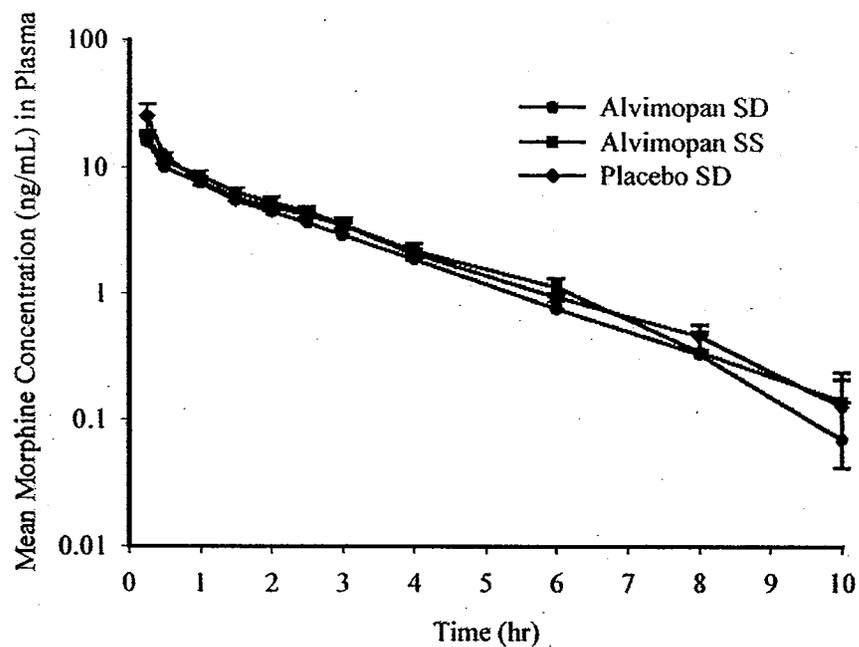
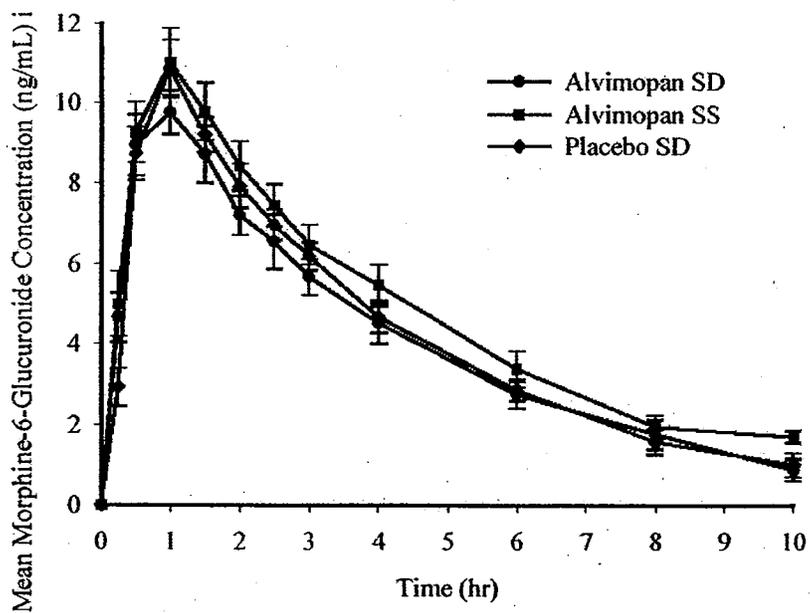


Figure 8: Mean (\pm SE) Morphine 6-glucuronide Concentrations (ng/mL)



**Table 29:
Pharmacokinetic Parameters of Morphine in the Presence and Absence of Alvimopan**

Parameter for Morphine	Treatment Group			ANOVA p-value ^b
	Placebo SD	Alvimopan SD	Alvimopan SS	
C(0)^a (ng/mL)				
Mean±SD	81.12±148.11	25.63±10.79	27.40±11.96	0.1855 ^c
%CV	182.6	42.1	43.6	
Geometric Mean	38.76	23.85	25.51	
t½λz (hr)				
Mean±SD	2.12±1.04	1.80±0.57	1.84±0.41	0.3433
%CV	49.0	31.6	22.0	
Geometric Mean	1.97	1.71	1.80	
λz (hr)				
Mean±SD	0.371±0.114	0.425±0.147	0.393±0.082	0.3758
%CV	30.7	34.6	20.9	
Geometric Mean	0.352	0.405	0.385	
AUC(0-∞)^a (hr*ng/mL)				
Mean±SD	42.01±23.01	29.69±9.10	34.95±9.60	0.0653 ^c
%CV	54.8	30.6	27.5	
Geometric Mean	38.31	28.67	33.85	
CL (mL/min)				
Mean±SD	1391±573	1804±593**	1514±455	0.0186
%CV	41.2	32.9	30.1	
Geometric Mean	1261	1691	1443	
Vss (L)				
Mean±SD	181±79	226±67**	213±66	0.0439
%CV	43.9	29.7	30.9	
Geometric Mean	151	215	203	

^a The log-transformed values for C(0) and AUC(0-∞) were used in the statistical analyses.

^b Indicates statistical significance (p<0.05) for a particular parameter among all groups using SAS PROC GLM and ANOVA.

^c Differences in log-transformed values are in geometric mean.

** Indicates statistical significance (p<0.05) compared to the placebo SD group by post-hoc testing.

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Table 30: PK parameters of 6-morphine glucuronide in the presence and absence of alvimopan

Parameter for 6-M-G	Treatment Group		
	Placebo SD	Alvimopan SD	Alvimopan SS
C_{max} (ng/mL)			
Mean±SD	10.88±2.21	10.08±1.93	11.40±2.42
%CV	20.3	19.1	21.2
Geometric Mean	10.69	9.89	11.16
T_{max} (hr)			
Mean±SD	1.1±0.2	1.1±0.3	1.2±0.5
%CV	15.1	27.0	40.3
Geometric Mean	1.0	1.0	1.1
Median	1.0	1.0	1.0
Range	(1.0-1.5)	(0.5-1.5)	(1.0-2.5)
t_{1/2}λ_z (hr)			
Mean±SD	3.08±0.92	3.11±0.65	3.97±2.70
%CV	30.0	21.0	68.1
Geometric Mean	2.98	3.05	3.54
λ_z (1/hr)			
Mean±SD	0.240±0.057	0.231±0.046	0.208±0.058
%CV	23.9	20.0	27.9
Geometric Mean	0.233	0.227	0.196
AUC(0-∞) (hr*ng/mL)			
Mean±SD	50.36±13.63	47.74±14.63	58.39±12.74
%CV	27.1	30.6	21.8
Geometric Mean	48.82	45.86	57.15

2.4.9 What other co-medications are likely to be administered to the target patient population? What drug-drug interaction information is available for these comedications?

Anesthetics and opioids other than morphine are likely to be administered to the target patient population. No pharmacokinetic drug-drug interaction information is available for these drugs when given with alvimopan.

2.4.10 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are coadministered?

A drug interaction study with morphine showed a lower mean morphine C₀ (↓66%) and AUC. However, it appears that the results might not be accurate in view of the high variability observed with the extrapolated morphine C₀ when morphine was coadministered with placebo. In addition, clinical data indicated that the interaction, if any, was not clinically significant.

2.4.11 Are there any medications that should be contraindicated in patients receiving alvimopan?

Undetermined

2.4.12 Are there other drugs that may have a significant pharmacokinetic interaction when coadministered with alvimopan?

In vitro studies suggested that both alvimopan and ADL 08-0011 may be P-gp substrates. Therefore, P-gp inhibitors may increase plasma concentrations of alvimopan and ADL 08-0011.

2.4.13 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions?

There are several unresolved questions:

- a. Formation of ADL 08-0011: The sponsor postulates that ADL 08-0011 is produced by gut microflora and aided by enterohepatic recycling of alvimopan. There are some nonclinical evidence but no human data on biliary secretion of alvimopan.
- b. Induction potential of alvimopan and ADL 08-0011: The study for alvimopan was inadequate and no studies were conducted for ADL 08-0011.
- c. Alvimopan and ADL 08-0011 as P-gp substrates: The sponsor is encouraged to conduct an *in vivo* interaction study with a P-gp inhibitor.

2.4.14 What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

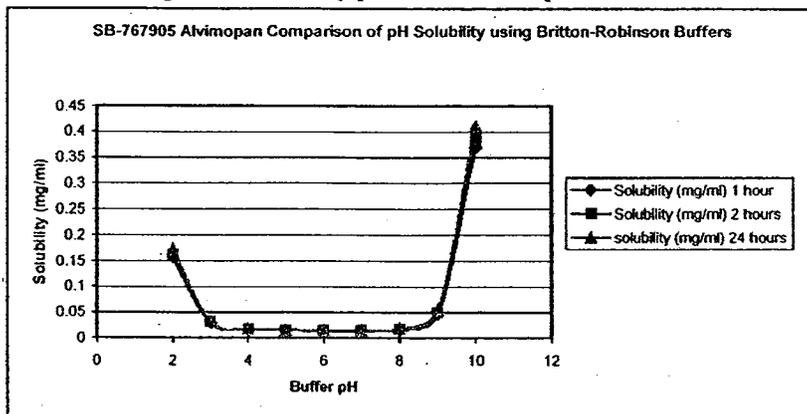
Several factors such as use of preoperative antibiotics were identified in the population PK analysis as having an effect on the alvimopan or ADL 08-0011 PK. Clinical data should be analyzed to determine the clinical significance of these findings.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

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Figure 9. Solubility profiles of alvimopan



Based on the studies with Caco-2 cells, alvimopan appears to have a low permeability. The B-to-A permeability of alvimopan (0.75×10^{-6} cm/s) was greater than the A-to-B permeability (0.26×10^{-6} cm/s), indicating that alvimopan was effluxed by P-gp pump at the Caco-2 cell membrane. According to the Biopharmaceutics Classification System (BCS), alvimopan can be categorized as a “Low Solubility-Low Permeability” (Class 4) drug.

Table 31:
Recovery and Permeability (10^{-6} cm/s) of Test Compounds

Compound Identification	Percent Recovery ^(a)			P _{app} ^(b) Blank	P _{app} A-to-B			P _{app} B-to-A			P _{app} ^{B-A} / P _{app} ^{A-B} Ratio ^(c)	Absorption Potential ^(d)	Significant Efflux ^(e)
	Blank	A-to-B	B-to-A		Rep. 1	Rep. 2	Avg	Rep. 1	Rep. 2	Avg			
ADL 08-0011										12.6	6.4	High	Yes
ADL 08-0011 + 2 μM GF120918										3.61	1.0	High	No
alvimopan										0.75	2.9	Low	No
alvimopan + 2 μM GF120918										0.31	1.1	Low	No

2.5.2 Are there differences between clinical formulation and to-be-marketed formulation?

No. The clinical formulation and to-be-marketed formulation are the same.

2.5.3 What is the effect of food on the bioavailability of the drug and what dosing recommendations should be made regarding administration in relation to meals?

Food effect was evaluated in a crossover study in which subjects were administered a single 12-mg dose of alvimopan under both fasted and fed conditions and 21 subjects completed the study.

Alvimopan: High fat meal decreased the rate and extent of absorption of alvimopan (AUC: 79.2%; C_{max}: 62.0%) and prolonged the mean T_{max} (3.1 hr vs. 1.9 hr).

ADL 08-0011: The sampling time of 48 hours was too short for ADL 08-0011. The mean C_{max} values for ADL 08-0011 between fed and fasted states were about equal, but the T_{max} for ADL 08-0011 was reached later under fed conditions. For about half the subjects, C_{max} was observed at 48 hours. Since 48 hours was the last sampling time, ADL 08-0011 concentrations could have continued to increase and the actual T_{max} may have been longer in some of the subjects. Thus, the C_{max} and T_{max} could not be accurately determined. This was also true for AUC.

This drug is to be administered to patients immediately before or after surgery. These patients are unlikely to be on high fat meal. The effect of light meal on the pharmacokinetics of alvimopan and ADL 08-0011 has not been studied. However, clinical trials were conducted without restrictions on meal times. Therefore, the label does not need to have any particular language on meal times relative to dosing times.

Table 32: Mean alvimopan and ADL 08-0011 PK parameters under fast and fed conditions

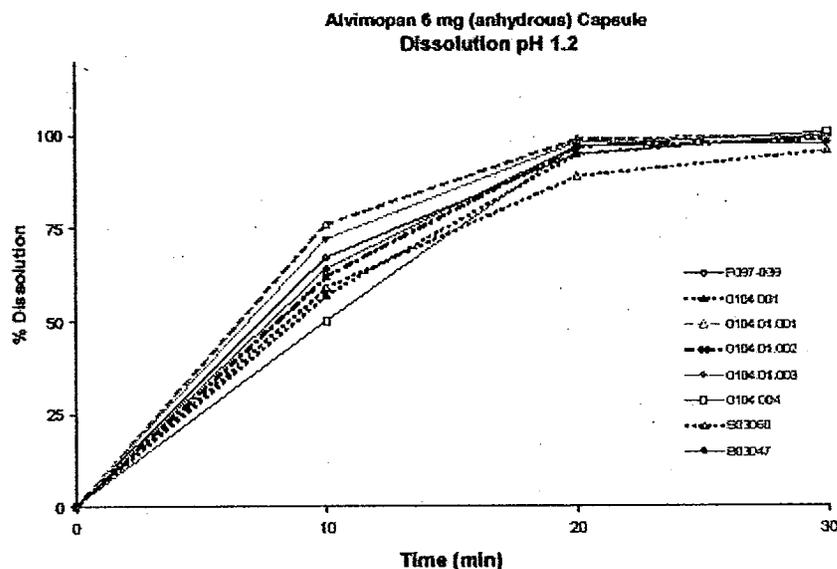
PK Parameter	Analyte			
	Alvimopan		ADL 08-0011	
	Fed State N=21	Fasted State N=21	Fed State N=21	Fasted State N=21
C_{max} (ng/mL)				
Mean ±SD	6.83 ± 2.25	11.96 ± 6.32	6.5 ± 3.5	6.6 ± 3.8
(CV%)	(32.9)	(52.9)	(54.1)	(57.8)
Geometric Mean	6.48	10.21	5.5	5.33
T_{max} (hr)				
Mean ±SD	3.1 ± 0.7	1.9 ± 0.7	38.4 ± 12.1	31.3 ± 16.1
(CV%)	(22.6)	(35.1)	(31.4)	(51.6)
Geometric Mean	3.0	1.8	34	26.2
Median	3.0	1.5	36.0	36.0
(Range)	(2.0-4.0)	(1.0-3.0)	(2.0-48.0)	(9.0-48.0)
t_{1/2} (hr)				
Mean ±SD	8.0 ± 9.0	5.3 ± 5.4	--	--
(CV%)	(112.4)	(102.0)	--	--
Geometric Mean	5.3	3.9	--	--
Clinically Relevant t% (hr)				
Mean ±SD	2.0 ± 0.9	2.4 ± 0.6	--	--
(CV%)	38.7	(28.6)	--	--
Geometric Mean	2.3	1.9	--	--
AUC(0-last) (hr*ng/mL)				
Mean ±SD	35.9 ± 11.1	50.6 ± 26.6	150.8 ± 82.4	150.6 ± 83.4
(CV%)	(30.8)	(52.6)	(54.6)	(55.4)
Geometric Mean	34.1	44.0	127.6	126.9
AUC(0-∞) (hr*ng/mL)				
Mean ±SD	39.9 ± 14.0	53.1 ± 27.8	--	--
(CV%)	(34.9)	(52.3)	--	--
Geometric Mean	37.6	46.6	--	--

2.5.4 Has the Applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Proposed Dissolution Method: 900 mL, 0.1 N HCl
Paddle, 50 rpm
Proposed Specification: NLT (Q) in 20 min.

The proposed specification does not appear to be discriminating for quality control purposes as many batches approached complete dissolution at 20 minutes. The sponsor was requested to provide dissolution profiles, including the 15-minute time point, for further evaluation. It is unclear whether other dissolution media were explored before selecting 0.1N HCl.

Fig. 10: Dissolution profiles of Entereg Capsules in 0.1N HCl



2.6 Analytical Section

2.6.1 How are the active moieties measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In the clinical pharmacology and biopharmaceutics studies, plasma concentrations of both alvimopan and ADL 08-0011 were determined. Total (free + bound) drug concentrations for both alvimopan and ADL 08-0011 were measured since protein binding was linear over the therapeutic concentration range.

Assays were performed at one of two sites: either at [REDACTED] (Studies 114, 116, 117 & 118) or [REDACTED] (other studies). The methods used were similar but the lower limit of quantification (LLQ) was 0.1 ng/mL for the assays conducted at [REDACTED] and 0.25 ng/mL for the assays conducted at [REDACTED].

For the assays at [REDACTED] plasma samples, spiked with an internal standard [REDACTED] were extracted using [REDACTED]. The solvent was [REDACTED]. The resulting extract is analyzed using a [REDACTED] column [REDACTED]. Detection is by MS/MS using a [REDACTED] Mass Spectrometer. For the mass spectrometric detection, the following transitions

were monitored: 425→218 for alvimopan, 368→218 for ADL 08-0011, and 278→218 for . Urine samples were assayed for alvimopan and ADL 08-0011 by an assay procedure similar to that used for plasma.

Table 34: Validation results of HPLC/MS/MS methods for assay of alvimopan and ADL 08-0011 in plasma and urine samples

Parameter	Alvimopan			
	Plasma	Urine	Plasma	Urine
LOQ, ng/mL	0.25	0.25	0.1	50
Linearity	0.25-250	0.25-250	0.1 - 50	50-5000
Accuracy (%)				
Intra-day	101.6 – 115.2	84.4 – 114.1	92.0 - 104.2	96.0-100.8
Inter-day	102.8 – 108.0	94.8 – 99.7	94.0 - 102.5	93.7 – 99.6
Precision (%CV)				
Intra-day	9.7% (0.25 ng/mL) 1.6–6.9% (others)	10.3% (0.25 ng/mL) 1.8-3.5% (others)	12.0% (0.1 ng/mL) 2.5-3.2% (others)	2.0 – 4.5%
Inter-day	NA (0.25 ng/mL) 3.7–5.0% (others)	NA (0.25 ng/mL) 4.3-9.5% (others)	12.8% (0.1 ng/mL) 5.9-10.5% (others)	3.3 - 5.5%
Specificity	No interferences			
Stability	stable at: RT, 24 hrs; -70°C, up to freeze-thaw cycles			
ADL 08-0011				
Parameter	Plasma	Urine	Plasma	Urine
LOQ, ng/mL	0.25	0.25	0.1	50
Linearity	0.25-250	0.25-250	0.1 - 50	50-5000
Accuracy				
Intra-day	91.6 – 103.6	94.8 - 99.7	97.0 – 103.6	94.1 – 99.3
Inter-day	96.8 – 104.0	95.9 - 99.2	93.0 - 106.8	95.9 – 99.2
Precision (%CV)				
Intra-day	11.0% (0.25 ng/mL) 3.3–8.4% (others)	5.3% (0.25 ng/mL) 2.4-5.2% (others)	10.3% (0.1 ng/mL) 3.4-5.8% (others)	2.6-6.7%
Inter-day	NA (0.25 ng/mL) 4.5–6.2% (others)	NA (0.25 ng/mL) 4.1-10.0% (others)	16.1% (0.1 ng/mL) 1.2-8.8% (others)	2.8–9.1%
Specificity	No interferences			
Stability	stable at: RT, 24 hrs; -70°C, up to freeze-thaw cycles			

3. APPENDIX

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Draft Labeling

Deliberative Process

3.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-775	Brand Name	Entereg	
OCPB Division (I, II, III)	II	Generic Name	Alvimopan	
Medical Division	Division of Gastrointestinal and Hematological Drug Products	Drug Class	-Receptor antagonist	
OCPB Reviewers	Sue-Chih Lee	Indication(s)	Postoperative Ileus	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Capsules	
Date of Submission	6/25/04 4/8/05	Proposed Dosing Regimen	12 mg at 30 min to 5 hrs prior to surgery 12 mg BID beginning the day after surgery for up to 7 days	
Estimated Due Date of OCPB Review	June 30, 2005	Route of Administration	Oral	
Medical Division Due Date	July 1, 2005	Sponsor	Adolor	
PDUFA Due Date	July 28, 2005	Priority Classification	1S	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	2	2	
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	2	1	
Patients-				
single dose:	X	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1	1	
In-vitro:	X	3	3	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:	x	2	2	
PD:				
Phase 2:	x	3	3	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1	1	
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	x	2	2	Mixed
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVVC):				
Bio-wavier request based on BCS				
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study	X	1	1	
Nonclinical studies		3	3	
Total Number of Studies		31	30	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is there a need to further characterize how ADL 08-0011 is formed? How much information can be deciphered from special population studies?			
Other comments or information not included above	Efficacy is an issue.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-775, HFD-870 (Electronic Entry or Lee), HFD-180 (Malandro), HFD-870 (Doddapaneni, Hunt, Malinowski),

**This is a representation of an electronic record that was signed electronically and
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/s/

Sue Chih Lee
7/11/05 03:05:13 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/11/05 03:58:28 PM
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