

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-775

STATISTICAL REVIEW(S)

Memorandum of Statistical Consultation

NDA/Serial Number: NDA 21-775 (Serial 000, dated August 9, 2007)
Applicant: Adolor Corporation
Product: Entereg (alvimopan 12 mg) Capsules
Indication: To accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis
Statistical Team: Sonia Castillo, Ph.D., Statistical Reviewer, Division of Biometrics 3
Michael Welch, Ph.D., Team Leader, Division of Biometrics 3
Clinical Team: Marjorie Dannis, M.D., Medical Reviewer, Division of Gastroenterology Products
Ruyi He, M.D., Team Leader, Division of Gastroenterology Products
Project Manager: Tom Moreno
Key Words: Complete Response, Safety Issues, NDA review

This submission provides Applicant responses to the following three information requests from the Division of Gastroenterology Products:

- Approvable Action letter, November 3, 2006 – Response to request to submit the 12 month safety findings (including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events) from Study SB767905/014 (Study 014) for review when they become available.
- Discussion and Meeting Minutes of the face-to-face meeting of December 7, 2006 - Response to request to submit finalized, quality assessed/quality controlled databases in order to assess the potential impact of the numerical increase for alvimopan treated patients compared to placebo in cardiovascular serious adverse events seen in the opioid-induced bowel dysfunction (OBD) Study 014 on the proposed short term use of alvimopan in POI. Also requested more complete data on the severe CV events, such as EKG strips and troponin levels and assessments of CV symptoms; and analyses of CV events in both POI and OBD populations, and short term (<14 days) and long-term (>14 days) population.
- Discussion in Telephone Conference of May 29, 2007 – Response to request to submit analyses and safety conclusions for the reported increase in the number of neoplasms and fractures in Study 014.

This record of consultation presents the tables and graphics that I generated at the request of the Clinical Reviewer. These items were used in the clinical evaluation of this submission and in the clinical presentation at an Advisory Committee Meeting held on January 23, 2008. The submission is fully electronic and is located at \\Cdsub1\N21775\N 000\2007-08-09.

**Appears This Way
On Original**

DEATH AND CARDIOVASCULAR EVENTS RELATIVE RISK TABLES FOR OBD AND POI STUDIES

Table 1
Number (%) of Deaths and Cardiovascular Events by Treatment in the Total POI Population

		Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	13 (0.50)	9 (0.66)	0.76 (0.33, 1.72)
	• Death from cardiovascular events	4 (0.15)	2 (0.15)	1.05 (0.22, 4.88)
	Subjects with cardiovascular events* (total)	51 (1.95)	39 (2.86)	0.68 (0.45, 1.03)
	• Ischemic events	17 (0.65)	14 (1.03)	0.64 (0.32, 1.27)
	• <i>Fatal</i>	<i>2 (0.08)</i>	<i>0 (0.0)</i>	<i>- (0.27, -)</i>
	• Other serious cardiovascular events	39 (1.49)	29 (2.12)	0.70 (0.44, 1.13)
	• <i>Fatal</i>	<i>2 (0.08)</i>	<i>2 (0.15)</i>	<i>0.52 (0.09, 2.96)</i>

Source: Statistical Reviewer's calculation using sponsor Table 9 on pages 41 to 44 of the POI CV safety report.

Ischemic events include the following fatal and non-fatal events: MI, unstable angina, and cerebro-vascular accident.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and cardiac arrest.

* The total number of cardiovascular events in each group is one less than the sum of each major category due to the following subjects: **Alvimopan** subject 14CL314-25-00025 had non-fatal MI and non-fatal congestive heart failure / **Alvimopan** subject 14CL314-36-00240 had non-fatal MI and non-fatal congestive heart failure / **Alvimopan** subject 14CL302-61-01173 had non-fatal cerebro-vascular accident and non-fatal congestive heart failure / **Alvimopan** subject 14CL314-26-00260 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Alvimopan** subject 14CL308-03-01041 had non-fatal cardiac arrest and non-fatal serious arrhythmia / **Placebo** subject 14CL308-13-01235 had non-fatal MI, unstable angina, and non-fatal congestive heart failure / **Placebo** subject 14CL302-06-01056 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Placebo** subject 14CL313-38-38001 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Placebo** subject GSK001-62-01289 had non-fatal serious arrhythmia and non-fatal cardiac arrest.

Includes studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Alvimopan group includes the following alvimopan doses: 1 mg (N=27), 3 mg (N=35), 6 mg (N=898), and 12 mg (N=1650).

Amended Table 1
Number (%) of Deaths and Cardiovascular Events by Treatment in the Total POI Population

		Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	13 (0.50)	9 (0.66)	0.76 (0.33, 1.72)
	• Death from cardiovascular events	4 (0.15)	2 (0.15)	1.05 (0.22, 4.88)
	Subjects with cardiovascular events* (total)	50 (1.92)	39 (2.86)	0.67 (0.44, 1.01)
	• Ischemic events	17 (0.65)	14 (1.03)	0.64 (0.32, 1.27)
	• <i>Fatal</i>	<i>2 (0.08)</i>	<i>0 (0.0)</i>	<i>- (0.27, -)</i>
	• Other serious cardiovascular events	39 (1.49)	29 (2.12)	0.70 (0.44, 1.13)
	• <i>Fatal</i>	<i>2 (0.08)</i>	<i>2 (0.15)</i>	<i>0.52 (0.09, 2.96)</i>

Source: Statistical Reviewer's calculation using sponsor Table 9 on pages 41 to 44 of the POI CV safety report.

Ischemic events include the following fatal and non-fatal events: MI, unstable angina, and cerebro-vascular accident.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and cardiac arrest.

* The total number of cardiovascular events in each group is one less than the sum of each major category due to the following subjects: **Alvimopan** subject 14CL314-25-00025 had non-fatal MI and non-fatal congestive heart failure / **Alvimopan** subject 14CL314-36-00240 had non-fatal MI and non-fatal congestive heart failure / **Alvimopan** subject 14CL302-61-01173 had non-fatal cerebro-vascular accident and non-fatal congestive heart failure / **Alvimopan** subject 14CL314-26-00260 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Alvimopan** subject 14CL308-03-01041 had non-fatal cardiac arrest and non-fatal serious arrhythmia / **Alvimopan** subject GSK001-02-00022 had non-fatal arrhythmia and non-fatal MI / **Placebo** subject 14CL308-13-01235 had non-fatal MI, unstable angina, and non-fatal congestive heart failure / **Placebo** subject 14CL302-06-01056 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Placebo** subject 14CL313-38-38001 had non-fatal congestive heart failure and non-fatal serious arrhythmia / **Placebo** subject GSK001-62-01289 had non-fatal serious arrhythmia and non-fatal cardiac arrest.

Includes studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Alvimopan group includes the following alvimopan doses: 1 mg (N=27), 3 mg (N=35), 6 mg (N=898), and 12 mg (N=1650).

Table 2
Number (%) of Deaths and Cardiovascular Events by Treatment in the Non-Cancer OBD Population

		Alvimopan N=1728 n (%)	Placebo N=790 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	4 (0.23)	2 (0.25)	0.91 (0.17, 4.98)
	• Death from cardiovascular events	2 (0.12)	0 (0.0)	- (0.24, -)
	Subjects with cardiovascular events* (total)	21 (1.22)	4 (0.51)	2.40 (0.87, 6.67)
	• Ischemic events	14 (0.81)	3 (0.38)	2.13 (0.66, 6.92)
	• <i>Fatal</i>	1 (0.06)	0 (0.0)	- (0.12, -)
	• Other serious cardiovascular events	8 (0.46)	2 (0.25)	1.83 (0.44, 7.60)
	• <i>Fatal</i>	1 (0.06)	0 (0.0)	- (0.12, -)

Source: Statistical Reviewer's calculation using sponsor Table 1 on page 9 of the OBD CV safety report.

Ischemic events include the following fatal and non-fatal events: MI, unstable angina, and cerebro-vascular accident.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and sudden death.

* The total number of cardiovascular events in each group is one less than the sum of each major category due to the following subjects: **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal congestive heart failure / **Placebo** subject 012 060006 6053 had non-fatal MI and non-fatal congestive heart failure.

Includes studies SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, and 13C304

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=197), 0.5 mg BID (N=1000), and 1 mg BID (N=130).

Table 3
Number (%) of Deaths and Cardiovascular Events by Treatment in the Non-Cancer OBD Study SB-767905/014

		Alvimopan N=538 n (%)	Placebo N=267 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	2 (0.37)	2 (0.75)	0.50 (0.09, 2.80)
	• Death from cardiovascular events	1 (0.19)	0 (0.0)	- (0.13, -)
	Subjects with cardiovascular events (total)	14 (2.60)	0 (0.0)	- (1.83, -)
	• Ischemic events	11 (2.05)	0 (0.0)	- (1.44, -)
	• <i>Fatal</i>	1 (0.19)	0 (0.0)	- (0.13, -)
	• Other serious cardiovascular events	3 (0.56)	0 (0.0)	- (0.39, -)

Source: Statistical Reviewer's calculation using sponsor Table 2 on page 10 of the OBD CV safety report.

Ischemic events include the following fatal and non-fatal events: MI, Unstable angina, and cerebro-vascular accident.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure and serious arrhythmia.

Note: Alvimopan group includes the following alvimopan dose and regimen: 0.5 mg BID (N=538).

Table 4
Number (%) of Deaths and Cardiovascular Events by Treatment in the Long-Term (>14 days) OBD Population (with Study 007)

		Alvimopan N=2049 n (%)	Placebo N=911 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	24 (1.17)	5 (0.55)	2.13 (0.85, 5.40)
	• Death from cardiovascular events	5 (0.24)	1 (0.11)	2.22 (0.34, 14.35)
	Subjects with cardiovascular events* (total)	26 (1.27)	7 (0.77)	1.65 (0.74, 3.71)
	• Ischemic events	14 (0.68)	5 (0.55)	1.24 (0.47, 3.32)
	• <i>Fatal</i>	1 (0.05)	0 (0.0)	- (0.12, -)
	• Other serious cardiovascular events	14 (0.68)	3 (0.33)	2.08 (0.64, 6.73)
	• <i>Fatal</i>	4 (0.20)	1 (0.11)	1.78 (0.27, 11.83)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report.

Includes studies SB-767905/007, SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Ischemic events include the following fatal and non-fatal events: MI, Unstable angina, and cerebro-vascular.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and sudden death.

* The total number of cardiovascular events in each group is less than the sum of each major category due to the following subjects: **Alvimopan** subject 008 0246881347 had death from serious arrhythmia and non-fatal congestive heart failure / **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal congestive heart failure / **Placebo** subject 012 060006 6053 had non-fatal MI and non-fatal congestive heart failure.

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=248), 3 mg BID (N=55), and 8 mg BID (N=53).

Table 5
Number (%) of Deaths and Cardiovascular Events by Treatment in the Long-Term (>14 days) OBD Population (without Study 007)

		Alvimopan N=1888 n (%)	Placebo N=860 n (%)	Relative Risk (asymptotic 95% CI)
All cases	All cause death (total)	24 (1.27)	5 (0.58)	2.19 (0.87, 5.53)
	• Death from cardiovascular events	5 (0.26)	1 (0.12)	2.28 (0.35, 14.70)
	Subjects with cardiovascular events* (total)	26 (1.38)	6 (0.70)	1.97 (0.84, 4.66)
	• Ischemic events	14 (0.74)	4 (0.46)	1.59 (0.55, 4.60)
	• <i>Fatal</i>	1 (0.05)	0 (0.0)	- (0.12, -)
	• Other serious cardiovascular events	14 (0.74)	3 (0.35)	2.13 (0.66, 6.89)
	• <i>Fatal</i>	4 (0.21)	1 (0.12)	1.82 (0.27, 11.12)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report.

Includes studies SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Ischemic events include the following fatal and non-fatal events: MI, Unstable angina, and cerebro-vascular.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and sudden death.

* The total number of cardiovascular events in each group is less than the sum of each major category due to the following subjects: **Alvimopan** subject 008 0246881347 had death from serious arrhythmia and non-fatal congestive heart failure / **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal congestive heart failure / **Placebo** subject 012 060006 6053 had non-fatal MI and non-fatal congestive heart failure.

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=195).

DISTRIBUTION OF CARDIOVASCULAR EVENTS TABLES FOR OBD AND POI STUDIES

OBD STUDIES

All Studies ≥ 14 Days

All CV Events

Days	Placebo (n=6)	Alvimopan (n=26)
14 or less	3	5
15 to 30	0	3
31 to 90	2	10
91 to 180	0	6
181 or more	1	2

Ischemic Events Only (MI, Angina, CVA)

Days	Placebo (n=4)	Alvimopan (n=13)
14 or less	1	1
15 to 30	0	0
31 to 90	2	8
91 to 180	0	3
181 or more	1	1

All Non-Cancer Pain Studies

All CV Events

Days	Placebo (n=4)	Alvimopan (n=21)
14 or less	2	3
15 to 30	0	1
31 to 90	2	9
91 to 180	0	6
181 or more	0	2

Ischemic Events Only (MI, Angina, CVA)

Days	Placebo (n=3)	Alvimopan (n=13)
14 or less	1	1
15 to 30	0	0
31 to 90	2	8
91 to 180	0	3
181 or more	0	

Study 014

All CV Events

Days	Placebo (n=0)	Alvimopan (n=14)
14 or less	0	0
15 to 30	0	0
31 to 90	0	7
91 to 180	0	5
181 or more	0	2

Ischemic Events Only (MI, Angina, CVA)

Days	Placebo (n=0)	Alvimopan (n=11)
14 or less	0	0
15 to 30	0	0
31 to 90	0	7
91 to 180	0	3
181 or more	0	1

POI STUDIES

All CV Events

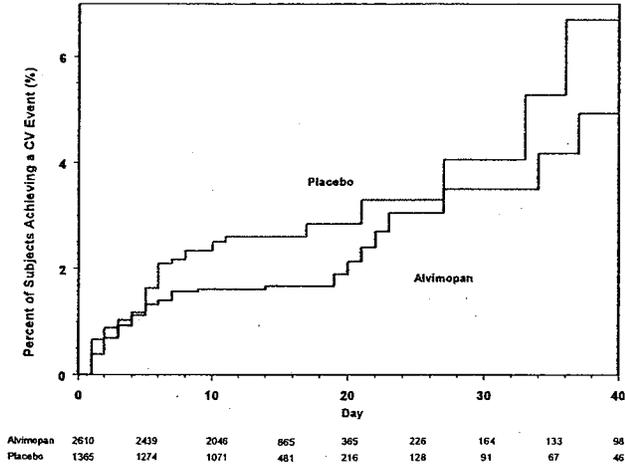
Days	Placebo (n=39)	Alvimopan (n=50)
3 or less	14	24
4 to 6	14	12
7 to 10	5	5
11 to 20	2	3
21 to 30	2	4
31 or more	2	2

Ischemic Events Only (MI, Angina, CVA)

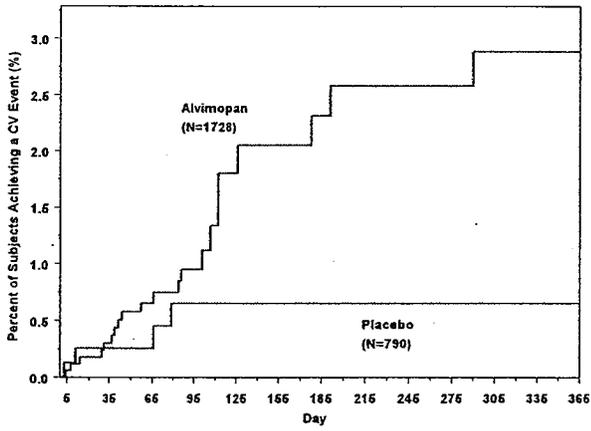
Days	Placebo (n=14)	Alvimopan (n=17)
3 or less	6	5
4 to 6	5	3
7 to 10	1	5
11 to 20	0	1
21 to 30	2	2
31 or more	0	1

TIME TO CARDIOVASCULAR EVENT GRAPHICS FOR OBD AND POI STUDIES

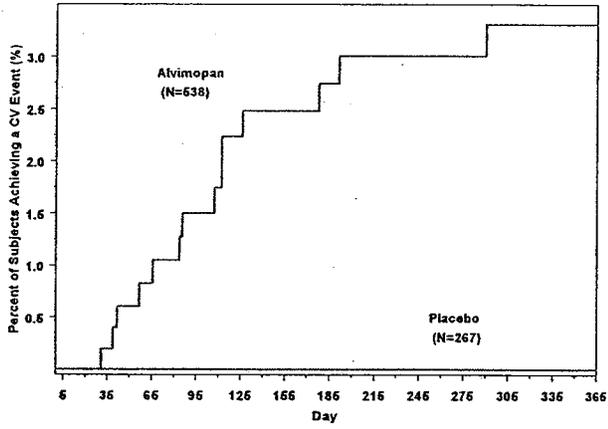
Kaplan-Meier Estimate of Time to a CV Event for POI Studies



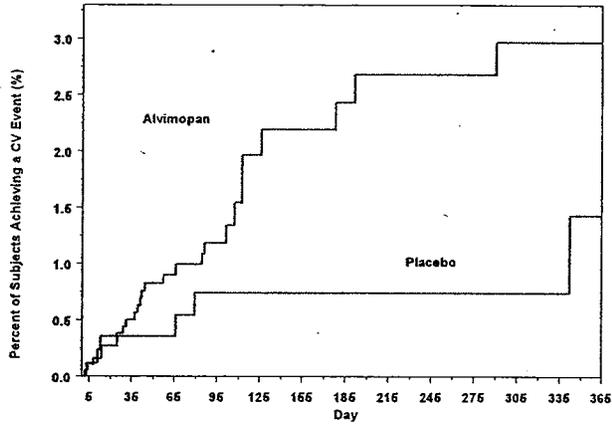
Kaplan-Meier Estimate of Time to a CV Event for Non-Cancer OBD Studies



Kaplan-Meier Estimate of Time to a CV Event for Study 014



Kaplan-Meier Estimate of Time to a CV Event for All OBD Studies (≥ 14 Days)



Alvimopan	1888	1603	1075	978	435	418	398	372	361	349	336	328	302
Placebo	860	733	523	465	206	195	185	171	165	158	149	145	135

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

/s/

Sonia Castillo
4/15/2008 03:41:53 PM
BIOMETRICS

Mike Welch
4/16/2008 03:19:44 PM
BIOMETRICS



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

(ADDENDUM)

NDA: 21-775 /Mouse and Rat Studies
Drug Name: SB-767905-KW (Entereg™ (alvimopan))
Applicant: Adolor Corporation
Date(s):
Response received: February 2, 2008
Report completed: February 6, 2008
Biometrics Division: Biometrics Division VI
Statistical Reviewer: Ling Chen, Ph.D.
Concurring Reviewers: Karl Lin, Ph.D.

Medical Division: Division of Gastroenterology Products
Pharmacologist: Chakraborti, Tamal K, Ph.D.
Regulatory Manager: Matthew Scherer
Keywords: NDA review, carcinogenicity, Dose response

Background Information

A statistical review of the carcinogenicity studies of Entereg® (alvimopan) Capsules in this NDA submission was done by this reviewer earlier. The results of the carcinogenicity studies were discussed at the Executive CAC meeting on December 4, 2007. The Executive CAC committee discovered a discrepancy in the incidence rates of thymoma (epithelial) in the thymus of male rats between those obtained and reported in the statistical review report by this reviewer from the tumor data set submitted for statistical review and those presented in the sponsor hard copy report of the NDA submission. The incidence rates of the tumor type obtained by this reviewer were 3 of 60, 0 of 60, 0 of 60, 2 of 60 and 3 of 60 for Group 1, 2, 3, 4 and 5, respectively, versus 0 of 57, 0 of 60, 0 of 60, 0 of 58, and 1 of 58, respectively, presented in the study report for the pharmacology /toxicology review (Table 7, page 161 of the study report). The Executive CAC asked the sponsor to explain the big discrepancy in the tumor incidence rates. The sponsor responded to information request of January 17 2008 by Executive CAC committee on January 25, 2008. Dr. Tamal K Chakraborti, the reviewing pharmacologist of this NDA, has asked this reviewer to examine the explanation for the tumor data discrepancy submitted by the sponsor. This addendum to my previous statistical review report contains the results of my examination of the sponsor's response to the ECAC information request.

Reviewer's Examination Results

In its response to the information request by Executive CAC committee, the sponsor indicated that the electronic tumor data contained in the SAS transport file and submitted to the FDA was created directly from the sponsor's data set stored in a Microsoft Excel file; that the incidence rates of this tumor type reported in NDA hard copy report were based on the data in the Excel file; and that the tumor data in the Excel file were correct.

The sponsor also indicated that its examination of the Excel spreadsheet derived from the SAS transport file failed to find an explanation why the missing tissues should have appeared to be associated with thymoma (epitheial) leading to the discrepancy noted by the Agency.

Attached below is a table listing the animals with this tumor type and with non-examined organ/tissue by dose groups obtained from SAS xpt file from the data set of the sponsor's original submission.

It has been clarified that the numeric code '3' in ORGANEXM column was used to identify when the tissue in question was not examined. The reviewer re-examined the original Rat dataset submitted by the sponsor on August 9, 2007. The following is the extracted data table from original tumor dataset for thymus.

STUDYNUM	ANIMLNUM	SEX	DOSEGP	TUMORNAM	TUMORCOD	ORGANEXM
BVR389	2	M	1		46	3
BVR389	12	M	1		46	3
BVR389	15	M	1		46	3
BVR389	196	M	5		46	3
BVR389	201	M	5		46	3
BVR389	254	M	6	B-THYMOMA (EPITHELIAL)	46	1
BVR389	285	M	6		46	3
BVR389	292	M	6		46	3

A correct dataset should not have data for the variables TUMORNAM and TUMORCOD for an organ/tissue that was not examined on an animal (i.e., the value for the variable ORGANEXM for the organ/tissue is 3). Obviously, the sponsor wrongly recoded tumor code for those animals with unexamined thymus tissue.

The reviewer corrected the original tumor data in the Rat dataset and reran the Peto trend test on the corrected data. The result from Peto's trend test shows that the dose response in incidence of this tumor type is not statistically significant.

Male Rats

Organ Name	Tumor Name	Water	Vehicle	100 mg/kg/d	200 mg/kg/d	500 mg/kg/d	P-Value (Exact)
THYMUS	B-THYMOMA(EPITHELIAL)	0	0	0	0	1	>0.025

Results of Re-analysis of the Rat Study

This reviewer has re-performed the analysis using the corrected data and found that there was no significant tumor finding in Rat tumor study.

Ling Chen, Ph.D.
Mathematical Statistician
DB6/OB

Concur: Karl Lin, Ph.D.
Team leader, DB6/OB

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

/s/

Ling Chen
2/8/2008 12:34:22 PM
BIOMETRICS

Karl Lin
2/8/2008 02:30:48 PM
BIOMETRICS
Concur with review



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA: 21-775 /Mouse and Rat Studies
Drug Name: SB-767905-KW (Entereg™ (alvimopan))
Applicant: Adolor Corporation
Date(s):
Data received: September 17, 2007
Report completed: December 12, 2007
Biometrics Division: Biometrics Division VI
Statistical Reviewer: Ling Chen, Ph.D.
Concurring Reviewers: Karl Lin, Ph.D.

Medical Division: Division of Gastroenterology Products
Pharmacologist: Chakraborti, Tamal K, Ph.D.
Regulatory Manager: Matthew Scherer
Keywords: NDA review, carcinogenicity, Dose response

Table of Contents

List of Tables.....	2
1. Background	3
2. Mouse Study.....	3
2.1 Sponsor’s analyses.....	3
2.1.1 Survival analysis	3
2.1.2 Tumor data analysis	5
2.2 Reviewer’s analyses.....	6
2.2.1 Survival analysis	6
2.2.2 Tumor data analysis	7
2.2.3 Reviewer’s findings	8
3. Rat Study	9
3.1 Sponsor’s analyses.....	9
3.1.1 Survival analysis	10
3.1.2 Tumor Data Analysis	10
3.2 Reviewer’s analyses.....	11
3.2.1 Survival analysis	11
3.2.2 Tumor data analysis	11
3.2.3 Reviewer’s findings	12
4. Summary	13
Appendix I.....	29
Appendix II.....	30
Reference.....	32

List of Tables

Table 1: Analysis of Mortality Data for Male Mice by Treatment and Time	14
Table 2: Analysis of Dose-Mortality Trend for Male Mice	15
Table 3: Report on Test for Positive Linear Dose-Tumor Trends in Male Mice	16
Table 4: Analysis of Mortality Data for Female Mice by Treatment and Time.....	18
Table 5: Analysis of Dose-Mortality Trend for Female Mice.....	18
Table 6: Report on Test for Positive Linear Dose-Tumor Trends in Female Mice.....	19
Table 7: Analysis of Mortality Data for Male Rats by Treatment and Time.....	21
Table 8: Analysis of Dose-Mortality Trend for Male Rats	21
Table 9: Report on Test for Positive Linear Dose-Tumor Trends in Male Rats	22
Table 10: Analysis of Mortality Data for Female Rats by Treatment and Time	24
Table 11: Analysis of Dose-Mortality Trend for Female Rats.....	24
Table 12: Report on Test for Positive Linear Dose-Tumor Trends in Female Rats.....	25

List of Figures

Figure 1: Kaplan-Meier Survival Functions for Male Mice.....	27
Figure 2: Kaplan-Meier Survival Functions for Female Mice	27
Figure 3: Kaplan-Meier Survival Functions for Male Rats.....	28
Figure 4: Kaplan-Meier Survival Functions for Female Rats	28

1. Background

SB-767905-KW is the dihydrate form of SB-767905, an opioid mu receptor antagonist. All doses and concentrations are expressed in terms of the parent compound, SB-767905.

The Sponsor performed both Mouse and Rat studies to evaluate the carcinogenicity potential of the test substance, SB-767905-KW. The duration of study was 104 weeks for male mice. The duration of study for female mice was 100 or 101 weeks due to survival in female fell below 15 animals in low dose (100 mg/kg/day) group and in vehicle control group at weeks 101 and 102 respectively. All surviving female mice in low dose group were killed in Week 101, and all remaining female mice from all groups were killed in Weeks 102/103.

2. Mouse Study

The objective of this study was to determine the effects of SB-767905-KW on the incidence and morphology of tumors in a 104 week oral (gavage) dose study in CD-1 mice.

Groups of mice (60/sex/group) were given 0 (purified water), 0 (vehicle), 100, 1000 or 4000 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia (10 mL/kg) by oral (gavage) administration once daily for up to 104 weeks. Animals were housed singly in individually ventilated cages throughout the treatment period.

Survival in the female group given 100 mg/kg/day fell below 15 animals in Week 101; therefore all surviving females in this group were killed in Week 101.

Survival in the vehicle control female group fell below 15 in Week 102; therefore all remaining females from all groups were killed in Weeks 102/103.

2.1 Sponsor's analyses

2.1.1 Survival analysis

Male and female data were analyzed separately. For the purposes of the analysis, females dosed at 100 mg/kg/day were considered to have been killed at the same time as the other female groups.

Survival probability functions were estimated by the Kaplan-Meier technique. Survival curves were compared up to the start of the terminal kill phase. Permutational tests for both an increasing and a decreasing dose response in mortality were performed across the vehicle control and the treated groups, using the dose levels as weighting coefficients, in

accordance with the IARC annex. One directional pairwise tests of the treated groups against the vehicle control group were also performed. The vehicle and water controls were compared using two-sided tests.

There were 379 decedents during the study (168 males and 211 females). The distribution and statistical analysis of these decedents are presented in the following table:

Sex	Type of death	Group					Results (P-values)				
							1-sided tests for increasing dose response				2-sided tests
		1 (C)	2 (L)	3 (I)	4 (H)	5 (W)	C,L,I,H	C v L	C v I	C v H	C v W
M	Accident	2	1	0	0	1	1.00	.425	1.00	1.00	.032*
	Dead or Moribund	42	41	25	24	32					
	Terminal Kill	16	18	35	36	27					
	Total	60	60	60	60	60					
F	Accident	1	0	2	1	0	0.972	0.460	0.637	0.959	0.118
	Dead or Moribund	45	46	42	36	38					
	Terminal Kill	14	14	16	23	22					
	Total	60	60	60	60	60					

C = Vehicle control, L = Low dose (100 mg/kg/day), I = Intermediate dose (1000 mg/kg/day), H = High dose (4000 mg/kg/day), W = Water control

* P<0.05

The Sponsor's reported that

1. For tests of increasing dose response, none of the tests achieved statistical significance for either sex ($P \geq 0.05$ for all tests).
1. In tests for decreasing mortality, males demonstrate a decreasing dose response in mortality across the groups ($P < 0.001$); the mortality in animals dosed at 1000 or 4000 mg/kg/day was significantly lower than that in the vehicle control ($P < 0.001$ for both tests). For females, there was a significant decreasing dose response across the four groups ($P = 0.028$).
2. For comparisons of the two control groups, in males, the water control group demonstrated significantly lower mortality than the vehicle control group. ($P = 0.032$).
3. For females, there was no significant difference in mortality between the two control groups ($P \geq 0.05$).
4. The causes of demise were generally consistent with the usual pattern of deaths for mice of this strain.

5. Common non-neoplastic causes of demise included skin/appendage lesions, in males and females, urogenital tract lesions in males and haemorrhagic ovarian cyst in females.
6. Common neoplastic causes of demise included haemolymphoreticular and lung tumors in males and females.
7. There were no deaths where the cause of demise could be directly related to effects of SB-767905.

2.1.2 Tumor data analysis

Tissues were protocolled to be examined for all animals. The numbers of tumor bearing animals were analyzed, for tumor types found in at least three animals of the given sex. Tumors of similar histogenic origin were merged, as requested by the Pathologist (See the Sponsor's Table 21). Permutational tests for both an increasing and a decreasing dose response were performed across vehicle control to treated groups, using the dose levels as weighting coefficients, in accordance with the IARC annex. One directional pairwise tests of the treated groups against the vehicle control group were also performed. Vehicle control and water control were compared using two-sided tests.

Non-fatal tumors were analyzed using fixed intervals of 1 to 50 weeks, 51 to 80 weeks, 81 weeks to start of terminal kill and the terminal kill phase. The fatal and non-fatal results were combined in accordance with the IARC annex. Where the combined analysis was significant ($P < 0.05$) and there were three or more tumors in the groups of interest, separate analyses for fatal and non-fatal tumors were performed. Tumors of uncertain context were analyzed as both fatal and non-fatal.

Indication of a possible treatment effect was assessed on the basis of rare or common tumor type, in line with current FDA guidelines.

For tests of increasing dose response, the following tumor types gave rise to results that were statistically significant at the 5% level:

- (a) osteogenic tumor, in females
- (b) skin/appendage fibroblastic tumor, in females

With the classification for type (a) tumor being rare, and the classification for type (b) being common, the results of note are:

- Female osteogenic tumor, fatals and non-fatals combined, overall dose response ($P=0.015$)
- Female skin/appendage fibroblastic tumor, fatals and non-fatals combined, overall dose response ($P=0.002$)

The sponsor explained its neoplastic findings as follows:

Microscopic neoplastic findings in control and treated animals were generally consistent with the usual pattern of neoplasms in mice of this strain. The initial, non-statistical analysis of tumor data failed to identify any treatment-related neoplasms.

Additionally, there was a statistically significant higher incidence of skin/appendage fibroblastic and osteogenic tumors (both benign and malignant combined) in females dosed at 4000 mg/kg/day, when compared to the vehicle control group. In the case of the fibroblastic tumors, the incidence (8.3 %) fell within the historical control range (0 to 9.8 %) for this tumor in this mouse strain/sex in this laboratory and these are commonly encountered in this laboratory species. The apparent increased incidence is therefore considered not to be related to treatment with SB-767905.

The incidence of osteogenic tumors (6.7 %) fell outside the historical control range (0 to 2.9 %) for this tumor in this mouse strain/sex in this laboratory. However, it is important to note that the incidence in the concurrent water control group (3.3 %) was also greater than this maximum historical control incidence. Furthermore, the difference between the incidence in females receiving 4000 mg/kg/day and water controls was equal to the difference between the two control groups. For these reasons, the incidence of osteogenic tumors in females, dosed at 4000 mg/kg/day is considered not to be related to treatment with SB-767905. This conclusion is supported by the absence of a consistent benign/malignant status or site of origin and the absence of any degenerative, inflammatory or non-neoplastic proliferative lesions involving tissues in which the osteogenic tumors were recorded.

In addition, the sponsor reported that for both sexes, there was no statistically significant difference in tumor incidence between the vehicle control and the water control for any tumor type analyzed ($P \geq 0.05$) for all tests.

2.2 Reviewer's analyses

To verify the results of sponsor's analyses this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically. The link to the data set is

\\CDSESUB1\N21775\N_000\2007-08-09

2.2.1 Survival analysis

The summaries of the intercurrent mortality data are given in Tables 1 and 4 for males and females, respectively. Since the termination sacrifices were done in week 105 for males, and in week 101/102 for females, the time intervals 0-52, 53-78, 79-91, and 92-104 weeks were chosen for males, and 0-52, 53-78, and 79-100 for females in the survival analysis.

From Tables 1 it can be seen that the numbers of survivals in male mice at the end of study are 35 and 36 in the 1000 mg/kg/day and the 4000 mg/kg/day dose groups respectively. However, at the end of Week 104 only 25 males survived in vehicle control group. This unusual phenomenon did not occur in female groups (see Table 4). In female mice the number of survivals in the 4000 mg/kg/day dose group is still much higher than that in vehicle control group (23 versus 15). Because only 15 female mice left in Week 101 in vehicle control group, the study was terminated earlier than what was planned. The difference in survival between the 4000 mg/kg/day dose group and the vehicle control group could be much larger than what has observed if the study was not terminated early.

The survival function of mice was also estimated using the Kaplan-Meier product limit method. The Kaplan-Meier curves for survival mice are given in Figures 1 and 2 for males and females, respectively.

From Figure 1, it can be noticed that for male mice, the survival curves of treated groups departed from survival curves of both water control and vehicle groups as early as Week 45. The order of the curves in terms of decreasing survival shows a very similar phenomenon to what we observed in Table 1.

From Figure 2, one may see that the survival curves for control and treated groups are very similar. Approximately at Week 70, the survival curves started to drop down very quickly. The 4000 mg/kg/day dose group still performed better than the vehicle control, although the difference between two survival curves may not be statistical significant. One may also notice that the survival curve of water control group is a similar to that of the 4000 mg/kg/day group.

The homogeneity of survival distributions of three treated groups and the vehicle control group was tested separately for males and females using the Cox test (Cox, 1972) and the Kruskal-Wallis test (Gehan, 1965; Thomas, *al.*, 1977). Results of the tests are given in Tables 2 and 5 for males and females, respectively. The tests showed statistically significant differences in survivals across treatment groups in male mice by both the Cox test ($p=0.0000$) and the Kruskal-Wallis test ($p=0.0000$). The test results for dose-mortality trend from both the Cox test and Kruskal-Wallis test are also statistically significant ($p\leq 0.0001$).

2.2.2 Tumor data analysis

The dose response analysis in tumor incidence was performed using the Peto test (Peto, *al.*, 1980). The actual dose levels of treatment groups were used as the weights for the trend analysis. The tumor rates and the p-values of the tumor types tested for dose response relationship are listed in Tables 3 and 6 for males and females, respectively. The p-values reflect one-sided tests for increases in tumors with dose. Tumors of similar histogenic origin were merged based on the Sponsor's Table 21. (See Appendix I)

Adjustment for multiplicity for the trend testing was done using a significance level of 2.5% for rare tumors and 0.5% for common tumors because two species were studied. A rare tumor is defined as one in which the spontaneous tumor rate in the control group, or the published spontaneous tumor rate is less than or equal to 1%. Adjustment for multiple pairwise comparisons was done using a significance level 5% for rare tumors and 1% for common tumors (see Lin and Rahman, 1998). In the tests the vehicle control group was used.

The p-values listed in Tables 3 and 6 are from either exact tests or asymptotic tests based on whatever is appropriate. The check marks (☑) in these tables indicate statistically significant test results, based on the decision rule of Divisions of Biometrics in Office of Biostatistics of CDER/FDA.

This reviewer also performed pairwise comparisons between each treated group and the vehicle control group, and between water control group and the vehicle control group.

Findings from Peto's trend tests and pairwise comparisons are presented in next section.

2.2.3 Reviewer's findings

Based on the reviewer's analyses, the tumor types with statistically significant dose responses in incidence with respect to the combined control group are listed in following table:

Female Mice

Organ Name	Tumor Name	Vehicle	100 mg/kg/d	1000 mg/kg/d	4000 mg/kg/d	P-Value (Asymp.)
COMBINED	OSTEOGENIC TUMOR	0	0	1	4	0.0063
COMBINED	S/A FIBROBLASTIC TUMOR	0	0	0	5	0.0003
SKIN + SUBCUTIS	SARCOMA - NOS	0	0	0	3	0.0063

All significant findings in the pairwise comparisons are listed in the following two tables:

Male mice

Organ Name	Tumor Name	Vehicle	100 mg/kg/d	P-Value (Asymp.)
LIVER	HEPATOCELLULAR CARCINOMA	0	3	0.0295

Female Mice

Organ Name	Tumor Name	Vehicle	1000 mg/kg/d	P-Value (Asymp.)
MAMMARY GLAND	ADENOCARCINOMA	0	3	0.0313
OVARY	CYSTADENOMA	0	3	0.0379
Organ Name	Tumor Name	Vehicle	4000 mg/kg/d	P-Value (Asymp.)
COMBINED	OSTEOGENIC TUMOR	0	4	0.0424
COMBINED	S/A FIBROBLASTIC TUMOR	0	5	0.0212

It appears that there are more significant findings in the reviewer’s analyses than in the Sponsor’s analyses.

3. Rat Study

The objective of this study was to determine the effect of SB-767905-KW on the incidence and morphology of tumors in a 104 week oral gavage carcinogenicity study in F344 rats.

Groups of rats (60/sex/group) were given 0 (water), 0 (vehicle), 100, 200 or 500 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia at a dose volume of 5 mL/kg by oral (gavage) administration once daily for 104 weeks. In additional group of 60 female rats was given 30 mg/kg/day, at a dose volume of 3 mL/kg, for the same period. Animals were housed singly in individually ventilated cages throughout the treatment period.

3.1 Sponsor’s analyses

The Sponsor reported protocol deviations before discussing its study results. The following is part of the deviations related to tumor data analysis.

For analysis of tumor data, tumor types were selected for analysis on the basis of a numerical criterion. The reasoning was that tumor types not meeting this criterion would have so few tumors as to have no chance of finding statistically significant differences. The default criterion was “Only analyze the tumor type if there was a total of at least two animals with tumors over all groups (control and treatment).” For this study, the criterion was modified to “Only analyze the tumor type if there was a total of at least two animals with tumors over the treatment groups only (i.e. not including control).” Tumor data not meeting this criterion would also have no chance of attaining statistical significance and unnecessary extra analysis was thereby avoided.

The protocol states that "Survival data will be analyzed using a two-tailed logrank trend test... for an increase in mortality versus nominal dose level...". Since a two-tailed test was applied, the protocol reference to "an increase" is, strictly speaking, incorrect. Survival data were in fact analyzed using a two-tailed logrank trend test versus nominal dose level. The protocol states that "For incidental tumors, the strata will be calculated using the "ad hoc" method of Peto *et al* (1980)." In fact, pre-determined fixed-interval strata were used in this study. Both methods are accepted by the regulatory authorities, but the fixed-interval method yields intervals with a more even distribution of mortality.

These deviations are considered not to have affected the integrity or validity of the study.

3.1.1 Survival analysis

The total numbers of unscheduled death are as follows:

Sex	Type of Death	Weeks	Dose (mg/kg/day)					
			0 (W)	0 (V)	30	100	200	500
Male	Dead/Killed	1-52	0	0	-	0	0	0
		53-78	8	4	-	3	6	2
		79-92	14	12	-	8	10	15
		93-104	18	14	-	10	17	16
		Total	40	30	-	21	33	33
	Terminal kill	104	20	30	-	39	27	27
Survival (%)	78	87	93	-	95	90	97	
	Survival (%)	104	33	50	-	65	45	45
Female	Dead/Killed	1-52	0	0	0	0	0	0
		53-78	3	4	4	3	2	5
		79-92	6	8	5	9	7	5
		93-104	14	9	11	7	7	7
		Total	23	21	20	19	16	17
	Terminal kill	104	37	39	40	41	44	43
Survival (%)	78	95	93	93	95	97	92	
	Survival (%)	104	62	65	67	68	73	72

3.1.2 Tumor Data Analysis

The sponsor reported that there were no neoplastic findings associated with treatment with SB-767905.

3.2 Reviewer's analyses

To verify the results of sponsor's analyses this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically. The link to the data set is

\\CDSESUB1\N21775\N_000\2007-08-09

3.2.1 Survival analysis

The summaries of the intercurrent mortality data are given in Tables 7 and 10 for males and females, respectively. Since the termination sacrifices were done in week 105 for males and females, the time intervals 0-52, 53-78, 79-91, and 92-104 weeks were chosen for survival analysis.

The survival rates were estimated using the Kaplan-Meier product limit method. The Kaplan-Meier curves for death rate are given in Figures 3 and 4 for males and females, respectively. The homogeneity of survival among vehicle control, 30 mg/kg/day (female only), 100 mg/kg/day, 200 mg/kg/day, and 500 mg/kg/day dose groups were tested using the Cox test and Kruskal-Wallis test. Results of the tests for homogeneity of survival among vehicle control, and treated groups are given in Tables 8 and 11 for males and females, respectively. The tests showed no statistically significant differences in survivals among vehicle control, low (female only), medium, medium high and high dose groups in either sex.

3.2.2 Tumor data analysis

Positive dose response analysis was performed using the Peto's method. The actual dose levels of treatment groups were used as the weight for the trend analysis. The tumor rates and the p-values of the tumor types tested for dose response relationship are listed in Tables 9 and 12 for male and females, respectively. Pairwise comparisons between treated groups and vehicle control were performed using the survival adjusted Fisher exact test.

Adjustment for the multiple trend testing was done using a significance level of $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors. A rare tumor is defined as one in which the spontaneous rate in the control or the published spontaneous tumor rate is less than or equal to 1%. Adjustment for multiple pairwise comparisons was done using a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors.

The p-values listed in Tables 9 and 12 are from either exact test or asymptotic test based on whatever is appropriate. The check marks (☑) in these tables indicate statistically

significant test results, based on the decision rule of Divisions of Biometrics in Office of Biostatistics of CDER/FDA.

This reviewer also performed pairwise comparisons between each treated group and the vehicle control group, and between the vehicle control group and water control group.

Tumor combinations were based on tumor types used in the sponsor's analysis (see Appendix II).

Findings from Peto's trend tests and pairwise comparisons are presented in next section.

3.2.3 Reviewer's findings

Based on the reviewer's analysis, the tumor types with statistically significant dose responses in incidence with respect to the vehicle control group are listed in following tables:

Male Rats

Organ Name	Tumor Name	Vehicle	100 mg/kg/d	200 mg/kg/d	500 mg/kg/d	P-Value (Exact)
THYMUS	B-THYMOMA(EPITHELIAL).	0	0	2	3	0.0104

Female Rats

Organ Name	Tumor Name	Vehicle	30 mg/kg/d	100 mg/kg/d	200 mg/kg/d	500 mg/kg/d	P-Value (Exact)
THYROIDS	M-C-CELL CARCINOMA	0	1	0	0	3	0.0199

The significant finding in the pairwise comparisons is listed in the following table:

Female Rats

Organ Name	Tumor Name	Vehicle	100 mg/kg/d	P-Value (Exact)
CLITORAL GLANDS	B-ADENOMA	0	4	0.0238

4. Summary

In the submission dated August 9, 2007, the sponsor included reports of two animal carcinogenicity studies, one in mice and one in rats. The objective of this study was to determine the effects of SB-767905-KW on the incidence and morphology of tumors in a 104 week oral gavage dose studies in the CD-1 mouse and in the F344 rats.

Based on the sponsor's report, groups of mice (60/sex/group) were given 0 (purified water), 0 (vehicle), 100, 1000 or 4000 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia (10 mL/kg) by oral (gavage) administration once daily for up to 104 weeks. Animals were housed singly in individually ventilated cages throughout the treatment period. Survival in the female group given 100 mg/kg/day fell below 15 animals in Week 101; therefore all surviving females in this group were killed in Week 101. Survival in the vehicle control female group fell below 15 in Week 102; therefore all remaining females from all groups were killed in Weeks 102/103.

In Rat study, groups of rats (60/sex/group) were given 0 (water), 0 (vehicle), 100, 200 or 500 mg/kg/day SB-767905-KW in 10% (w/v) aqueous acacia at a dose volume of 5mL/kg by oral (gavage) administration once daily for 104 weeks. An additional group of 60 female rats was given 30 mg/kg/day, at a dose volume of 3 mL/kg, for the same period.

In the reviewer's analyses, the homogeneity tests showed statistically significant differences in survivals for only male mice across treatment groups. P-values from both Cox and Kruskal-Wallis tests are approximately zero. From Kaplan-Meier Survival Functions for male mice (see Figure 1), dose groups 1000 mg/kg/day and 4000 mg/kg/day survived much better than vehicle control group. This is an unusual phenomenon. The Peto's trend tests showed statistically significant dose responses in the incidence of SARCOMA-NOS in skin+subcutis, OSTEOGENIC tumor crossed organs, and S/A FIBROBLASTIC tumor crossed organs in female mice. The trend tests also showed statistically significant dose responses in the incidence of B-THYMONA (EPTIHELIAL) in thymus in male rats, and in the incidence of M-C-CELL CARCINOMA in thyroids in female rats. (The phrase "dose response" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.)

Besides the significant results for the tumor types found in trend tests, the reviewer also performed pairwise comparisons (vehicle control group versus each treated group and versus water control group). The tumor types with a significant increase in the incidence over the vehicle control are summarized in the following table.

Specie	Sex	Comparison	Organ Name	Tumor Name	p-value
Mice	M	Vehicle vs 100 mg/kg/d	Liver	Hepatocellular carcinoma	0.0295
Mice	F	Vehicle vs 1000 mg/kg/d	Mammary gland	Adenocarcinoma	0.0313

Mice	F	Vehicle vs 1000 mg/kg/d	Ovary	Cystadenoma	0.0379
Mice	F	Vehicle vs 4000 mg/kg/d	Combined	Osteogenic tumor	0.0424
Mice	F	Vehicle vs 4000 mg/kg/d	Combined	S/A Fibroblastic tumor	0.0212
Rats	F	Vehicle vs 100 mg/kg/d	Clitoral glands	B-Adenoma	0.0238

Ling Chen, Ph.D.
 Mathematical Statistician
 DB6/OB

Concur: Karl Lin, Ph.D.
 Team leader, DB6/OB

Table 1: Analysis of Mortality Data for Male Mice by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Water Control	0-52	60	5	55	91.7	8.3
	53-78	55	8	47	78.3	21.7
	79-91	47	11	36	60	40
	92-104	36	9	27	45	55
	FINALKILL 105-105	27	27	0		
Vehicle Control	0-52	60	6	54	90	10
	53-78	54	18	36	60	40
	79-91	36	11	25	41.7	58.3
	92-104	25	9	16	26.7	73.3
	FINALKILL 105-105	16	16	0		
100 mg/kg/day	0-52	60	10	50	83.3	16.7
	53-78	50	22	28	46.7	53.3
	79-91	28	4	24	40	60
	92-104	24	6	18	30	70
	FINALKILL 105-105	18	18	0		

1000 mg/kg/day	0-52	60	4	56	93.3	6.7
	53-78	56	2	54	90	10
	79-91	54	10	44	73.3	26.7
	92-104	44	9	35	58.3	41.7
	FINALKILL 105-105	35	35	0		
4000 mg/kg/day	0-52	60	4	56	93.3	6.7
	53-78	56	7	49	81.7	18.3
	79-91	49	3	46	76.7	23.3
	92-104	46	10	36	60	40
	FINALKILL 105-105	36	36	0		

Table 2: Analysis of Dose-Mortality Trend for Male Mice

Vehicle Control	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Departure from Trend	14.7600	0.0006	15.9018	0.0004
Dose-Mortality Trend	16.2170	0.0001	16.8581	0.0000
Homogeneity	30.9771	0.0000	32.7599	0.0000

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute.

**Appears This Way
On Original**

**Table 3: Report on Test for Positive Linear Dose-Tumor Trends in Male Mice
(Vehicle control)**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0	#1	-94	BLOOD VESSEL TUMOR	7	1	3	4	0.7100	0.7052
00	#2	-95	HISTIOCYTIC SARCOMA(Combine)	1	1	0	0	0.9484	0.8817
AB	ABDOMINAL CAVITY	623	HAEMANGIOSARCOMA	0	0	1	0	0.6762	0.6655
AD	ADRENAL	121	SUBCAPSULAR CELL ADENOMA	1	2	5	5	0.2148	0.2112
CC	CRANIAL CAVITY	691	MENINGIOMA	0	1	0	0	0.5000	0.1611
CT	CONNECTIVE TISSUE	86	HISTIOCYTIC SARCOMA	1	0	0	0	1.0000	0.8204
EA	EAR	420	HAEMANGIOMA	1	0	0	0	1.0000	0.8422
FE	FEMUR + MARROW	623	HAEMANGIOSARCOMA	1	0	0	1	0.5131	0.3449
HE	HAEMOLYMPHORETICULAR	-91	LYMPHOID TUMOR	3	5	10	3	0.9428	0.9380
HE	HAEMOLYMPHORETICULAR	146	MALIGNANT LYMPHOMA-LYMPHOBLAST	0	3	1	0	0.9163	0.9292
HE	HAEMOLYMPHORETICULAR	322	MALIGNANT LYMPHOMA - LYMPHOCYT	1	0	1	0	0.8963	0.8439
HE	HAEMOLYMPHORETICULAR	406	GRANULOCYTIC LEUKAEMIA	1	0	1	0	0.7608	0.7569
HE	HAEMOLYMPHORETICULAR	686	MALIGNANT MAST CELL TUMOUR	1	0	0	0	1.0000	0.8460
HE	HAEMOLYMPHORETICULAR	73	MALIGNANT LYMPHOMA - PLEOMORPH	2	2	8	3	0.7589	0.7524
HG	HARDERIAN GLAND	126	ADENOMA	7	5	6	6	0.7709	0.7690
KI	KIDNEY	608	TUBULAR CELL ADENOMA	0	0	1	0	0.6762	0.6655
LI	LIVER	-92	HEPATOCELLULAR TUMOR	9	14	19	15	0.7357	0.7400
LI	LIVER	123	HEPATOCELLULAR CARCINOMA	0	3	2	0	0.8877	0.9146
LI	LIVER	420	HAEMANGIOMA	2	1	1	2	0.5856	0.5583
LI	LIVER	623	HAEMANGIOSARCOMA	0	0	1	0	0.6522	0.6536
LI	LIVER	83	HEPATOCELLULAR ADENOMA	9	12	18	15	0.6427	0.6472
LU	LUNG	-93	ALVEOLAR EPITHELIAL TUMOR	19	9	24	18	0.7458	0.7479
LU	LUNG	169	BRONCHIOLO-ALVEOLAR CARCINOMA	7	3	4	13	0.0859	0.0794
LU	LUNG	37	BRONCHIOLO-ALVEOLAR ADENOMA	13	6	20	7	0.9781	0.9758
MU	MUSCLE	420	HAEMANGIOMA	1	0	0	0	1.0000	0.8066
PA	PANCREAS	581	ISLET CELL ADENOMA	0	0	1	1	0.3462	0.2565
PI	PITUITARY	126	ADENOMA	0	1	0	0	0.8476	0.8315
SK	SKIN + SUBCUTIS	118	SARCOMA - NOS	0	2	2	0	0.8438	0.8853
SK	SKIN + SUBCUTIS	610	SQUAMOUS CELL PAPILLOMA	0	0	0	1	0.3429	0.0889
SK	SKIN + SUBCUTIS	86	HISTIOCYTIC SARCOMA	0	1	0	0	0.7606	0.7753

SM	STERNUM + MARROW	623	HAEMANGIOSARCOMA	0	1	0	0	0.6327	0.6571
SP	SPLEEN	420	HAEMANGIOMA	1	0	0	1	0.4367	0.2287
ST	STOMACH	126	ADENOMA	0	2	0	0	0.9253	0.9137
TA	TAIL	576	FIBROMA	0	0	1	0	0.5714	0.6438
TE	TESTIS	256	INTERSTITIAL CELL ADENOMA	1	2	2	0	0.9408	0.9426
TE	TESTIS	420	HAEMANGIOMA	1	0	0	0	1.0000	0.7285
TE	TESTIS	670	RETE TESTIS ADENOMA	0	0	1	0	0.6762	0.6655
TO	TONGUE	610	SQUAMOUS CELL PAPILLOMA	0	0	1	0	0.6827	0.6691

*Appears This Way
On Original*

Table 4: Analysis of Mortality Data for Female Mice by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Water Control	0-52	60	6	54	90	10
	53-78	54	12	42	70	30
	79-101	42	20	22	36.7	63.3
	FINALKILL 102-103	22	22	0		
Vehicle Control	0-52	60	6	54	90	10
	53-78	54	18	36	60	40
	79-101	36	21	15	25	75
	FINALKILL 102-103	15	15	0		
100 mg/kg/day	0-52	60	8	52	86.7	13.3
	53-78	52	18	34	56.7	43.3
	79-100	34	18	16	26.7	73.3
	FINALKILL 101-101	16	16	0		
1000 mg/kg/day	0-52	60	10	50	83.3	16.7
	53-78	50	14	36	60	40
	79-101	36	20	16	26.7	73.3
	FINALKILL 102-103	16	16	0		
4000 mg/kg/day	0-52	60	9	51	85	15
	53-78	51	9	42	70	30
	79-101	42	19	23	38.3	61.7
	FINALKILL 102-103	23	23	0		

Table 5: Analysis of Dose-Mortality Trend for Female Mice

Vehicle Control	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Departure from Trend	0.2250	0.8936	0.3272	0.8491
Dose-Mortality Trend	2.6330	0.1047	1.7532	0.1855
Homogeneity	2.8580	0.4140	2.0804	0.5559

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute.

**Table 6: Report on Test for Positive Linear Dose-Tumor Trends in Female Mice
(Vehicle control)**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0	#1	-94	BLOOD VESSEL TUMOR	2	0	0	1	0.5782	0.4726
00	#2	-95	HISTIOCYTIC SARCOMA (combined)	4	1	3	4	0.3067	0.2975
000	#3	-96	OSTEOGENIC TUMOR	0	0	1	4	0.0129	0.0063 (⚠)
000	#4	-97	S/A FIBROBLASTIC TUMOR	0	0	0	5	0.0019	0.0003 (⚠)
BO	BONE	404	OSTEOSARCOMA	0	0	1	1	0.7500	0.7582
BO	BONE	501	OSSIFYING FIBROMA	1	0	0	0	1.0000	0.9214
CO	COLON	126	ADENOMA	0	0	1	0	0.5065	0.5667
FE	FEMUR + MARROW	677	OSTEOMA	0	0	0	1	0.3239	0.0791
HE	HAEMOLYMPHORETICULAR	-91	LYMPHOID TUMOR	5	11	8	9	0.5132	0.5254
HE	HAEMOLYMPHORETICULAR	146	MALIGNANT LYMPHOMA - LYMPHOBLAST	0	2	1	1	0.4941	0.5638
HE	HAEMOLYMPHORETICULAR	303	HISTIOCYTIC SARCOMA	2	1	2	0	0.9007	0.8991
HE	HAEMOLYMPHORETICULAR	322	MALIGNANT LYMPHOMA - LYMPHOCYT	0	1	1	1	0.3547	0.3908
HE	HAEMOLYMPHORETICULAR	338	MALIGNANT LYMPHOMA - PLASMACYT	0	1	0	0	0.7895	0.7894
HE	HAEMOLYMPHORETICULAR	406	GRANULOCYTIC LEUKAEMIA	0	1	0	0	0.7731	0.7867
HE	HAEMOLYMPHORETICULAR	73	MALIGNANT LYMPHOMA - PLEOMORPH	5	7	6	7	0.4673	0.4787
HG	HARDERIAN GLAND	-92	ADENOMA/CARCINOMA	4	3	5	6	0.1980	0.1909
HG	HARDERIAN GLAND	126	ADENOMA	4	3	4	6	0.1708	0.1623
HG	HARDERIAN GLAND	653	ADENOCARCINOMA	0	0	1	0	0.5493	0.6228
LI	LIVER	303	HISTIOCYTIC SARCOMA	0	0	0	1	0.2468	0.0452
LI	LIVER	83	HEPATOCELLULAR ADENOMA	1	1	0	1	0.6077	0.5351
LN	LYMPH NODE	472	HAEMANGIOMA	1	0	0	0	1.0000	0.7006
LU	LUNG	-93	ALVEOLAR EPITHELIAL TUMOR	7	10	6	8	0.5587	0.5710
LU	LUNG	169	BRONCHIOLO-ALVEOLAR CARCINOMA	1	6	3	3	0.6103	0.6410
LU	LUNG	37	BRONCHIOLO-ALVEOLAR ADENOMA	6	4	4	5	0.4672	0.4671
MA	MAMMARY GLAND	653	ADENOCARCINOMA	0	0	3	1	0.3061	0.3025
OV	OVARY	-98	SEX CORD/STROMAL TUMOR	0	2	0	1	0.5461	0.5577
OV	OVARY	428	CYSTADENOMA	0	0	3	3	0.0579	0.0483
OV	OVARY	472	HAEMANGIOMA	0	0	0	1	0.2468	0.0452
OV	OVARY	544	BENIGN LUTEOMA	0	2	0	0	0.8487	0.8814
OV	OVARY	559	LEIOMYOMA	0	0	1	0	0.5065	0.5667
OV	OVARY	688	BENIGN SEX CORD STROMAL TUMOUR	0	0	0	1	0.3239	0.0791

PA	PANCREAS	581	ISLET CELL ADENOMA	2	1	0	0	0.9879	0.9278
PI	PITUITARY	126	ADENOMA	3	1	2	2	0.6656	0.6516
PI	PITUITARY	711	SCHWANNOMA	0	0	1	0	0.5000	0.5671
SK	SKIN + SUBCUTIS	118	SARCOMA - NOS	0	0	0	3	0.0312	0.0063 !
SK	SKIN + SUBCUTIS	303	HISTIOCYTIC SARCOMA	1	0	0	0	1.0000	0.7848
SK	SKIN + SUBCUTIS	339	FIBROSARCOMA	0	0	0	1	0.2464	0.0448
SK	SKIN + SUBCUTIS	368	FIBROMA	0	0	0	1	0.2500	0.0464
SK	SKIN + SUBCUTIS	521	MALIGNANT BASAL CELL TUMOUR	1	0	0	0	1.0000	0.8716
SP	SPLEEN	472	HAEMANGIOMA	1	0	0	0	1.0000	0.7872
ST	STOMACH	610	SQUAMOUS CELL PAPILLOMA	1	0	0	0	1.0000	0.8152
ST	STOMACH	681	SQUAMOUS CELL CARCINOMA	1	0	0	0	1.0000	0.8152
TC	THORACIC CAVITY	404	OSTEOSARCOMA	0	0	0	1	0.2977	0.0670
TO	TONGUE	610	SQUAMOUS CELL PAPILLOMA	0	0	1	0	0.5111	0.5733
TY	THYROID	568	FOLLICULAR CELL ADENOMA	0	1	0	0	0.7403	0.7662
UT	UTERUS	-99	SMOOTH MUSCLE TUMOR	1	4	2	3	0.4555	0.4861
UT	UTERUS	303	HISTIOCYTIC SARCOMA	1	0	1	3	0.0761	0.0445
UT	UTERUS	516	STROMAL POLYP	4	6	1	0	0.9990	0.9939
UT	UTERUS	559	LEIOMYOMA	1	2	2	1	0.6722	0.7100
UT	UTERUS	569	LEIOMYOSARCOMA	0	2	0	2	0.2470	0.2283
UT	UTERUS	645	STROMAL SARCOMA	1	0	1	0	0.7795	0.7898
UT	UTERUS	653	ADENOCARCINOMA	1	0	0	0	1.0000	0.7848
UT	UTERUS	689	BENIGN GRANULAR CELL TUMOUR	0	0	0	1	0.3239	0.0791
UT1	CERVIX	516	STROMAL POLYP	0	0	0	1	0.3239	0.0791
UT1	CERVIX	559	LEIOMYOMA	0	1	0	0	0.7746	0.7967
VA	VAGINA	516	STROMAL POLYP	1	0	0	0	1.0000	0.8070

Note: The check mark ! indicates statistically significant test results, based on the decision rule of FDA,CDER,Divisions of Biometrics.

Appears This Way
On Original

Table 7: Analysis of Mortality Data for Male Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Water Control	53-78	60	8	52	86.7	13.3
	79-91	52	13	39	65	35
	92-104	39	19	20	33.3	66.7
	FINALKILL 105-107	20	20	0		
Vehicle Control	53-78	59	4	55	93.2	6.8
	79-91	55	11	44	74.6	25.4
	92-104	44	14	30	50.8	49.2
	FINALKILL 105-107	30	30	0		
100 mg/kg/day	53-78	60	3	57	95	5
	79-91	57	8	49	81.7	18.3
	92-104	49	10	39	65	35
	FINALKILL 105-107	39	39	0		
200 mg/kg/day	53-78	57	4	53	93	7
	79-91	53	9	44	77.2	22.8
	92-104	44	18	26	45.6	54.4
	FINALKILL 105-107	26	26	0		
500 mg/kg/day	53-78	60	2	58	96.7	3.3
	79-91	58	13	45	75	25
	92-104	45	18	27	45	55
	FINALKILL 105-107	27	27	0		

Table 8: Analysis of Dose-Mortality Trend for Male Rats

Vehicle Control	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Departure from Trend	4.0104	0.1346	3.8429	0.1464
Dose-Mortality Trend	1.2363	0.2662	0.7518	0.3859
Homogeneity	5.2467	0.1546	4.5946	0.2040

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute.

**Table 9: Report on Test for Positive Linear Dose-Tumor Trends in Male Rats
(Vehicle control)**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AB	ABDOMEN	1	M-OSTEOSARCOMA	0	1	0	0	0.6923	0.6472
AB	ABDOMEN	2	M-SARCOMA NOS	0	0	0	1	0.2297	0.0454
AD	ADRENALS	-91	B-PHAECHROMOCYTOMA /M-MALIGNA	2	7	4	5	0.3156	0.2976
AD	ADRENALS	4	B-PHAECHROMOCYTOMA	2	7	4	4	0.4712	0.4538
AD	ADRENALS	6	M-CORTICAL CARCINOMA	0	1	0	0	0.7521	0.6813
AD	ADRENALS	7	M-MALIGNANT PHAECHROMOCYTOMA	0	0	0	1	0.2231	0.0418
AT	ADIPOSE TISSUE	3	M-LIPOSARCOMA	0	0	1	0	0.6000	0.5559
BN	BRAIN	10	B-GRANULAR CELL TUMOUR	0	0	1	0	0.5366	0.5443
BN	BRAIN	11	M-MALIGNANT RETICULOSIS	0	0	0	1	0.2213	0.0412
BN	BRAIN	12	M-MENINGEAL SARCOMA	0	0	0	1	0.2393	0.0495
BO	BONE	9	M-SQUAMOUS CELL CARCINOMA	0	0	1	0	0.4344	0.4686
CO	COLON	32	B-ADENOMA	0	0	2	0	0.5886	0.5705
ED	EPIDIDYMIDES	14	M-MESOTHELIOMA	0	1	3	0	0.6266	0.5896
EE	EYES	15	B-SCHWANNOMA	1	0	0	0	1.0000	0.8477
HD	HEAD	19	B-SQUAMOUS PAPILLOMA	0	0	1	0	0.4344	0.4686
HG	HARDERIAN GLANDS	20	M-ADENOCARCINOMA	0	1	0	0	0.7667	0.7449
HP	HAEMATOPOIETIC TUMOUR	16	M-HISTIOCYTIC SARCOMA	0	0	2	1	0.1932	0.1712
HP	HAEMATOPOIETIC TUMOUR	17	M-LARGE GRANULAR CELL LYMPHOMA	30	26	34	35	0.1041	0.0985
JE	JEJUNUM	20	M-ADENOCARCINOMA	1	0	1	1	0.4696	0.4141
KI	KIDNEYS	21	M-RENAL LIPOSARCOMA	0	0	1	0	0.6000	0.5559
LI	LIVER	22	B-HEPATOCELLULAR ADENOMA	3	5	4	3	0.5334	0.5169
MA	MAMMARY AREAS	24	M-MAMMARY ADENOCARCINOMA	1	0	0	0	1.0000	0.8648
PA	PANCREAS	-92	B-ISLET CELL ADENOMA /M-ISLET	6	6	9	9	0.2282	0.2138
PA	PANCREAS	25	B-ISLET CELL ADENOMA	6	5	8	9	0.2002	0.1858
PA	PANCREAS	26	B-MIXED CELL ADENOMA	2	0	0	0	1.0000	0.9273
PA	PANCREAS	27	M-ISLET CELL CARCINOMA	0	1	1	0	0.5765	0.6097
PG	PREPUTIAL GLANDS	30	B-ADENOMA	1	1	0	1	0.5431	0.4919
PI	PITUITARY	28	B-ADENOMA, PARS DISTALIS	12	14	18	11	0.5948	0.5826
SB	SUBCUTIS	39	B-FIBROMA	6	7	3	5	0.7426	0.7287
SB	SUBCUTIS	40	B-LIPOMA	0	2	0	1	0.4038	0.3428
SB	SUBCUTIS	41	M-FIBROSARCOMA	0	1	1	0	0.5932	0.6207
SG	SALIVARY	20	M-ADENOCARCINOMA	1	0	0	0	1.0000	0.8569

	GLANDS								
SK	SKIN	33	B-KERATOACANTHOMA	1	0	0	0	1.0000	0.8602
SK	SKIN	35	B-SQUAMOUS CELL PAPILLOMA	1	1	1	0	0.8310	0.8163
SK	SKIN	36	M-BASAL CELL CARCINOMA	1	0	0	0	1.0000	0.8803
SP	SPLEEN	37	M-SARCOMA, UNDIFFERENTIATED	0	1	0	0	0.7541	0.6822
ST	STOMACH	35	B-SQUAMOUS CELL PAPILLOMA	0	2	0	1	0.4817	0.4245
SV	SEMINAL VESICLES	32	B-ADENOMA	2	2	0	0	0.9858	0.9602
TD	THYROIDS	-93	B-C-CELL ADENOMA/M-C-CELL CARC	11	12	8	3	0.9960	0.9936
TD	THYROIDS	47	B-C-CELL ADENOMA	11	12	8	2	0.9989	0.9977
TD	THYROIDS	48	B-FOLLICULAR CELL ADENOMA	1	0	2	0	0.7333	0.7318
TD	THYROIDS	49	M-C-CELL CARCINOMA	0	0	1	1	0.1427	0.0983
TL	TAIL	43	M-LEIOMYOSARCOMA	0	0	1	0	0.6000	0.5559
TS	TESTES	44	B-INTERSTITIAL (LEYDIG) CELL A	37	43	34	41	0.2266	0.2137
TX	THORAX	45	M-ANAPLASTIC CARCINOMA	0	0	0	1	0.3000	0.0788
TY	THYMUS	46	B-THYMOMA(EPITHELIAL)	0	0	2	3	0.0104	0.0060

Note: The check mark  indicates statistically significant test results, based on the decision rule of FDA.CDER.Divisions of Biometrics.

Appears This Way
On Original

Table 10: Analysis of Mortality Data for Female Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
Water Control	53-78	48	3	45	93.8	6.3
	79-91	45	6	39	81.3	18.8
	92-104	39	14	25	52.1	47.9
	FINALKILL 105-107	25	25	0		
Vehicle Control	53-78	48	2	46	95.8	4.2
	79-91	46	5	41	85.4	14.6
	92-104	41	11	30	62.5	37.5
	FINALKILL 105-107	30	30	0		
30 mg/kg/day	53-78	55	4	51	92.7	7.3
	79-91	51	4	47	85.5	14.5
	92-104	47	11	36	65.5	34.5
	FINALKILL 105-107	36	36	0		
100 mg/kg/day	53-78	54	3	51	94.4	5.6
	79-91	51	9	42	77.8	22.2
	92-104	42	7	35	64.8	35.2
	FINALKILL 105-107	35	35	0		
200 mg/kg/day	53-78	51	1	50	98	2
	79-91	50	6	44	86.3	13.7
	92-104	44	8	36	70.6	29.4
	FINALKILL 105-107	36	36	0		
500 mg/kg/day	53-78	54	5	49	90.7	9.3
	79-91	49	5	44	81.5	18.5
	92-104	44	7	37	68.5	31.5
	FINALKILL 105-107	37	37	0		

Table 11: Analysis of Dose-Mortality Trend for Female Rats

Vehicle Control	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Departure from Trend	0.5641	0.9046	0.6627	0.8819
Dose-Mortality Trend	0.3610	0.5480	0.2933	0.5881
Homogeneity	0.9251	0.9209	0.9560	0.9164

Note: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute.

**Table 12: Report on Test for Positive Linear Dose-Tumor Trends in Female Rats
(Vehicle control)**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR2	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENALS	2	B-CORTICAL ADENOMA	1	0	3	1	0	0.8152	0.8248
AD	ADRENALS	3	B-PHAECHROMOCYTOMA	0	1	0	1	2	0.0759	0.0581
AT	ADIPOSE TISSUE	1	B-LIPOMA	0	0	0	1	0	0.4195	0.4445
BC	BUCCAL CAVITY	7	M-SQUAMOUS CELL CARCINOMA	0	0	0	0	1	0.1724	0.0223
BN	BRAIN	5	M-ASTROCYTOMA	0	1	0	0	0	0.8276	0.7856
BN	BRAIN	6	M-OLIGODENDROGLIOMA	1	0	1	0	0	0.8103	0.8033
BO	BONE	4	M-OSTEOSARCOMA	0	0	1	0	0	0.6292	0.6641
CA	CAECUM	8	M-ADENOCARCINOMA	1	0	2	0	0	0.9031	0.8688
CT	CLITORAL GLANDS	9	B-ADENOMA	0	2	4	4	3	0.1878	0.1820
HD	HEAD	15	M-LEIOMYOSARCOMA	0	0	1	0	0	0.5000	0.5917
HP	HAEMATOPOIETIC TUMOUR	10	M-HISTIOCYTIC SARCOMA	0	1	0	0	1	0.3073	0.2405
HP	HAEMATOPOIETIC TUMOUR	11	M-LARGE GRANULAR CELL LYMPHOMA	18	27	14	16	16	0.9130	0.9108
HP	HAEMATOPOIETIC TUMOUR	12	M-MALIGNANT LYMPHOMA	2	0	0	0	0	1.0000	0.9080
HP	HAEMATOPOIETIC TUMOUR	13	M-MIXED LYMPHOMA	0	1	0	2	1	0.2494	0.2578
JE	JEJUNUM	16	M-ADENOCARCINOMA	2	1	2	0	0	0.9900	0.9639
KI	KIDNEYS	17	B-TUBULAR ADENOMA [B]/[M]	0	2	0	0	0	0.8993	0.8687
KI	KIDNEYS	17	B-TUBULAR ADENOMA	0	2	0	0	0	0.8993	0.8687
KI	KIDNEYS	18	M-RENAL LIPOSARCOMA	0	0	1	0	1	0.2188	0.1644
KI	KIDNEYS	19	M-RENAL MESENCHYMAL TUMOUR	1	0	0	0	0	1.0000	0.8304
KI	KIDNEYS	20	M-TUBULAR CARCINOMA	0	1	0	0	0	0.8276	0.7856
LI	LIVER	21	B-HEPATOCELLULAR ADENOMA	3	1	2	5	4	0.1377	0.1329
MA	MAMMARY AREAS	192	ADENOMA[B]/FIBROADENOMA[B]	9	14	17	12	10	0.8001	0.8004
MA	MAMMARY AREAS	22	B-MAMMARY ADENOMA	0	0	1	0	2	0.0821	0.0445
MA	MAMMARY AREAS	23	B-MAMMARY FIBROADENOMA	9	14	16	12	8	0.9038	0.9013
MA	MAMMARY AREAS	24	M-DUCTULAR CARCINOMA	1	0	0	0	0	1.0000	0.8253
MA	MAMMARY AREAS	25	M-MAMMARY ADENOCARCINOMA	0	0	1	1	1	0.1952	0.1876
OV	OVARIES	26	B-GRANULOSA CELL TUMOUR	1	0	0	0	1	0.3810	0.2782
PA	PANCREAS	27	B-ISLET CELL ADENOMA	2	0	1	1	1	0.5184	0.5357
PI	PITUITARY	28	B-ADENOMA, PARS DISTALIS	20	23	21	21	28	0.0920	0.0904
SB	SUBCUTIS	34	B-FIBROMA	0	1	0	0	1	0.3073	0.2405
SK	SKIN	31	B-KERATOACANTHOMA	0	0	2	0	0	0.7040	0.7180
SK	SKIN	32	B-SQUAMOUS CELL PAPILLOMA	0	1	0	1	0	0.5344	0.6310
ST	STOMACH	32	B-SQUAMOUS CELL PAPILLOMA	0	1	0	0	0	0.8276	0.7856
TD	THYROIDS	93	B-C-CELL ADENOMA/M-C-CELL CARC	4	6	6	8	10	0.0601	0.0553
TD	THYROIDS	94	B-FOLLICULAR CELL ADENOMA/M-FO	1	2	3	1	1	0.7379	0.7446
TD	THYROIDS	36	B-C-CELL ADENOMA	4	5	6	8	7	0.2277	0.2270
TD	THYROIDS	37	B-FOLLICULAR CELL ADENOMA	1	0	2	1	1	0.4569	0.4710
TD	THYROIDS	38	M-C-CELL CARCINOMA	0	1	0	0	3	0.0199	0.0077

NDA 21-775 CIT/Adolor corporation/SB-767905-KW/Mouse and Rats Studies

									!	
TD	THYROIDS	39	M-FOLLICULAR CELL CARCINOMA	0	2	1	0	0	0.8855	0.8755
UT	UTERUS	-95	M-ADENOCARCINOMA/B-ENDOMETRIAL	1	0	2	0	1	0.4617	0.4538
UT	UTERUS	16	M-ADENOCARCINOMA	0	0	2	0	1	0.3150	0.2789
UT	UTERUS	41	B-ENDOMETRIAL ADENOMA	1	0	0	0	0	1.0000	0.7969
UT	UTERUS	42	B-ENDOMETRIAL POLYP	11	10	17	12	12	0.5651	0.5692
UT	UTERUS	44	M-ANAPLASTIC CARCINOMA	0	1	0	0	0	0.7674	0.7442
UT	UTERUS	45	M-ENDOMETRIAL STROM. SARCOMA	0	2	0	0	1	0.4486	0.4438
UT	UTERUS	46	M-SCHWANNOMA	0	0	1	1	0	0.5066	0.5748
UX	UTERINE CERVIX	40	B-GRANULAR CELL TUMOUR	1	1	0	0	0	0.9599	0.8736

Note: The check mark ! indicates statistically significant test results, based on the decision rule of FDA.CDER.Divisions of Biometrics

Appears This Way
On Original

Figure 1: Kaplan-Meier Survival Functions for Male Mice

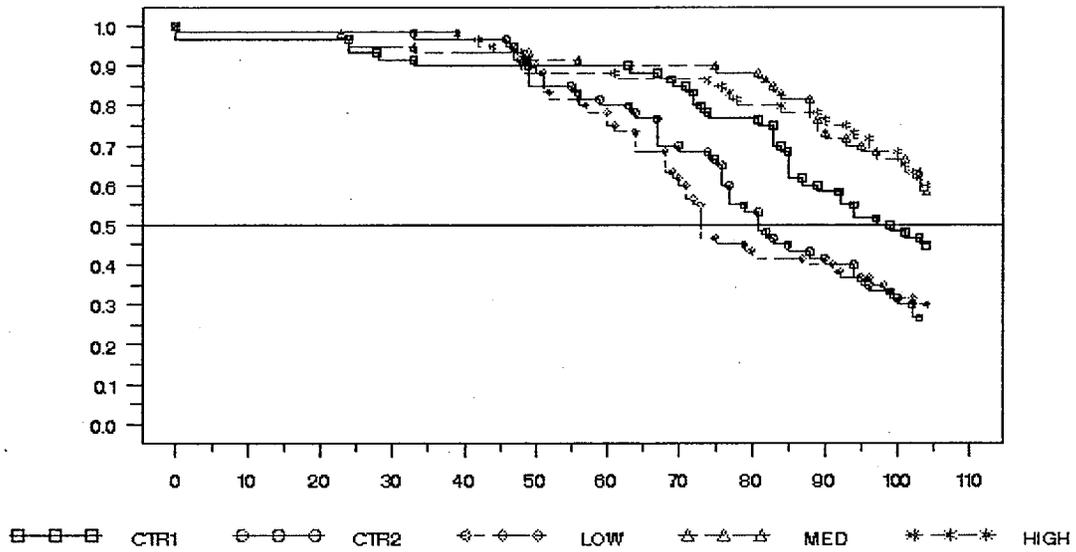


Figure 2: Kaplan-Meier Survival Functions for Female Mice

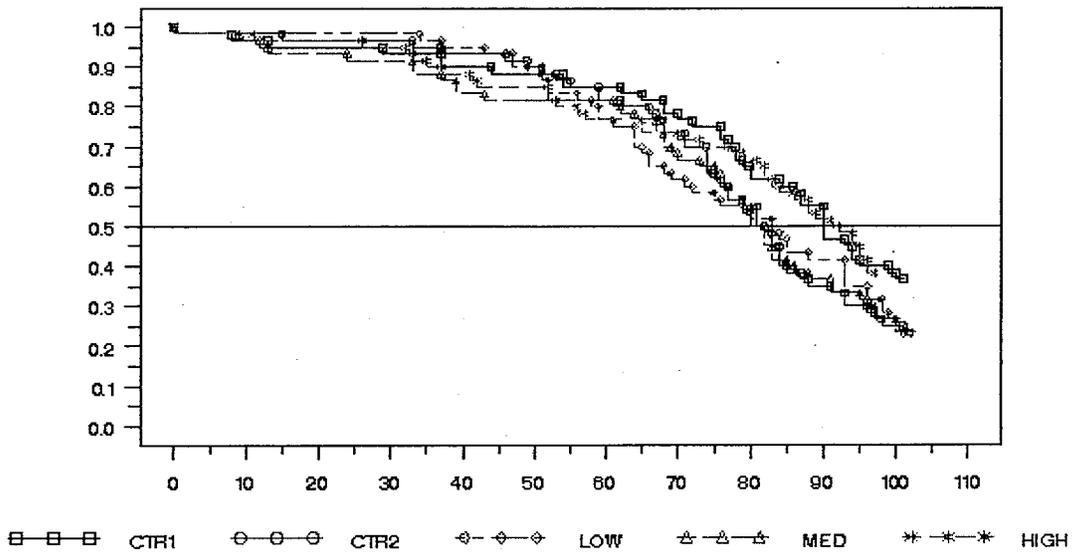


Figure 3: Kaplan-Meier Survival Functions for Male Rats

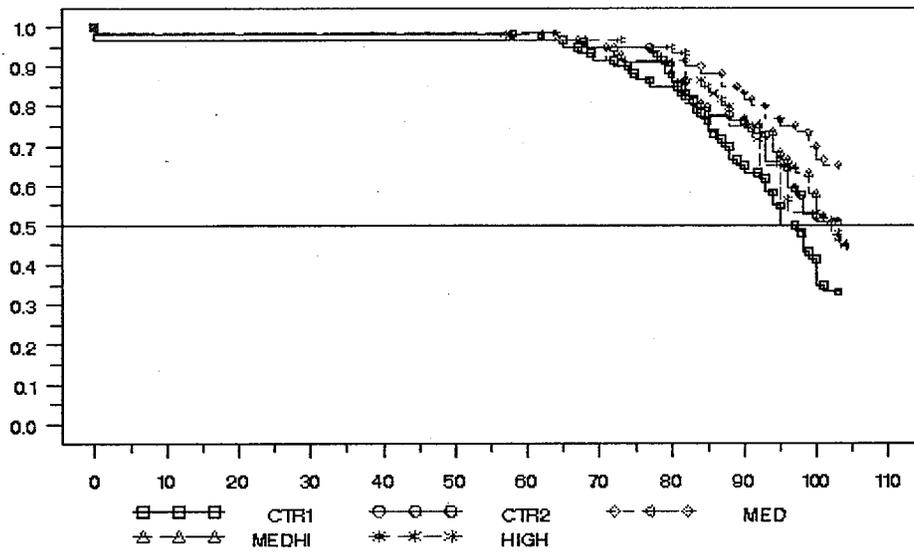
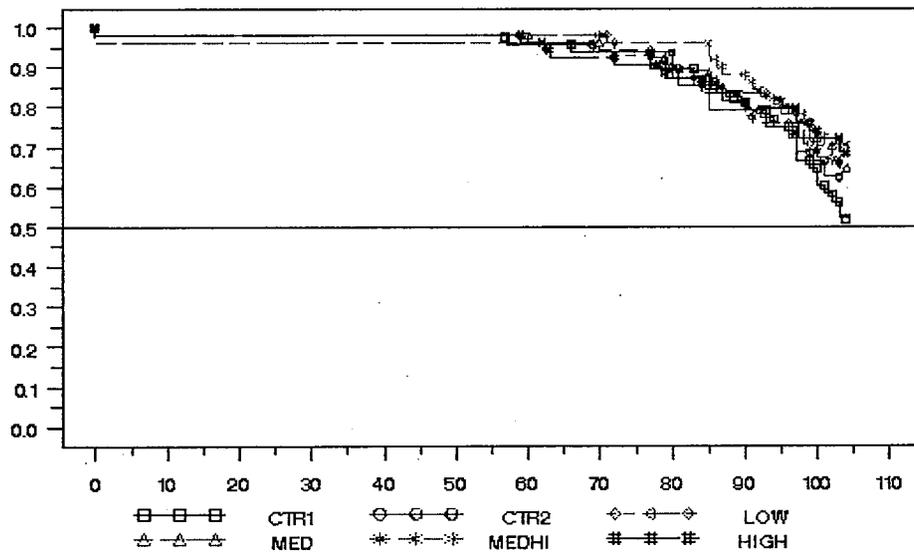


Figure 4: Kaplan-Meier Survival Functions for Female Rats



Appendix I

Table 21 Tumor statistics for Mice

Tumor types analyzed

Tissue

Type Tumor type Tissue Finding

AD B-SUBCAPSULAR CELL ADENOMA ADRENAL B-SUBCAPSULAR CELL ADENOMA
 HE M-HISTIOCYTIC SARCOMA HAEMOLYMPHORETICULAR M-HISTIOCYTIC SARCOMA
 HE M-GRANULOCYTTIC LEUKAEMIA HAEMOLYMPHORETICULAR M-GRANULOCYTTIC LEUKAEMIA
 MA M-ADENOCARCINOMA MAMMARY GLAND M-ADENOCARCINOMA
 OV B-CYSTADENOMA OVARY B-CYSTADENOMA
 PA B-ISLET CELL ADENOMA PANCREAS B-ISLET CELL ADENOMA
 PI B-ADENOMA PITUITARY B-ADENOMA
 TE B-INTERSTITIAL CELL ADENOMA TESTIS B-INTERSTITIAL CELL ADENOMA
 HE LYMPHOID TUMOUR HAEMOLYMPHORETICULAR M-MALIGNANT LYMPHOMA - LYMPHOCYTIC
 HAEMOLYMPHORETICULAR M-MALIGNANT LYMPHOMA - NOS
 HAEMOLYMPHORETICULAR M-MALIGNANT LYMPHOMA - PLASMACYTIC
 HAEMOLYMPHORETICULAR M-MALIGNANT LYMPHOMA - PLEOMORPHIC
 HAEMOLYMPHORETICULAR M-MALIGNANT LYMPHOMA-LYMPHOBLASTIC
 HG ADENOMA/CARCINOMA HARDERIAN GLAND B-ADENOMA
 HARDERIAN GLAND M-ADENOCARCINOMA
 LI HEPATOCELLULAR TUMOUR LIVER B-HEPATOCELLULAR ADENOMA
 LIVER M-HEPATOCELLULAR CARCINOMA
 LU ALVEOLAR EPITHELIAL TUMOUR LUNG B-BRONCHIOLO-ALVEOLAR ADENOMA
 LUNG M-BRONCHIOLO-ALVEOLAR CARCINOMA
 OV SEX CORD/STROMAL TUMOUR OVARY B-BENIGN LUTEOMA
 OVARY B-BENIGN SEX CORD STROMAL TUMOUR
 UT SMOOTH MUSCLE TUMOUR UTERUS B-LEIOMYOMA
 UTERUS M-LEIOMYOSARCOMA
 UT STROMAL TUMOUR UTERUS B-STROMAL POLYP
 UT STROMAL TUMOUR UTERUS M-STROMAL SARCOMA
 # BLOOD VESSEL TUMOUR ABDOMINAL CAVITY M-HAEMANGIOSARCOMA
 EAR B-HAEMANGIOMA
 FEMUR + MARROW M-HAEMANGIOSARCOMA
 LIVER B-HAEMANGIOMA
 LIVER M-HAEMANGIOSARCOMA
 LYMPH NODE B-HAEMANGIOMA
 MESENTERIC LYMPH NODE B-HAEMANGIOMA
 MUSCLE B-HAEMANGIOMA
 OVARY B-HAEMANGIOMA
 SPLEEN B-HAEMANGIOMA
 STERNUM + MARROW M-HAEMANGIOSARCOMA
 TESTIS B-HAEMANGIOMA
 # = Merged tissues
 # HISTIOCYTIC SARCOMA CONNECTIVE TISSUE M-HISTIOCYTIC SARCOMA
 LIVER M-HISTIOCYTIC SARCOMA
 SKIN + SUBCUTIS M-HISTIOCYTIC SARCOMA
 UTERUS M-HISTIOCYTIC SARCOMA
 # OSTEOGENIC TUMOUR BONE B-OSTEOMA
 BONE M-OSTEOSARCOMA
 FEMUR + MARROW B-OSTEOMA
 SPINAL CORD M-MALIGNANT OSTEOSARCOMA
 THORACIC CAVITY M-OSTEOSARCOMA
 # S/A FIBROBLASTIC TUMOUR SKIN + SUBCUTIS B-FIBROMA
 SKIN + SUBCUTIS M-FIBROSARCOMA
 SKIN + SUBCUTIS M-SARCOMA - NOS
 TAIL B-FIBROMA
 # = Merged tissues
 S/A = Skin/appendage

Appendix II

Rats

Males

Adrenals - Benign phaeochromocytoma
Adrenals - Benign phaeochromocytoma and malignant phaeochromocytoma combined
Epididymides - Malignant mesothelioma
Liver - Benign hepatocellular adenoma
Pancreas - Benign Islet cell adenoma
Pancreas - Malignant Islet cell carcinoma
Pancreas - Benign Islet cell adenoma and malignant Islet cell carcinoma combined
Pituitary - pars distalis - Benign adenoma
Preputial glands - Benign adenoma
Skin - Benign squamous cell papilloma
Stomach - Benign squamous cell papilloma
Testes - Benign interstitial (Leydig) cell adenoma
Thyroids - Benign C-cell adenoma
Thyroids - Malignant C-cell carcinoma
Thyroids - Benign C-cell adenoma and malignant C-cell carcinoma combined
Thyroids - Benign follicular cell adenoma
Thyroids - Benign follicular cell adenoma and malignant follicular cell carcinoma combined
Haematopoietic Tumour - Malignant large granular cell lymphoma
Haematopoietic Tumour - Malignant histiocystic sarcoma

Females

Adrenals - Benign phaeochromocytoma
Adrenals - Benign cortical adenoma
Clitoral glands - Benign adenoma
Kidneys - Malignant renal liposarcoma
Kidneys - Benign tubular adenoma
Kidneys - Benign tubular adenoma and malignant tubular carcinoma combined
Liver - Benign hepatocellular adenoma
Mammary areas - Benign fibroadenoma
Mammary areas - Benign mammary adenoma
Mammary areas - Benign mammary fibroadenoma and benign mammary adenoma combined
Mammary areas - Malignant mammary adenocarcinoma
Mammary areas - Benign mammary fibroadenoma, benign mammary adenoma and malignant mammary adenocarcinoma combined
Pancreas - Benign Islet cell adenoma
Pituitary - pars distalis - Benign adenoma
Skin - Benign squamous cell papilloma

Skin - Benign keratoacanthoma
Thymus - Benign thymoma (epithelial)
Thyroids - Benign C-cell adenoma
Thyroids - Malignant C-cell carcinoma
Thyroids - Benign C-cell adenoma and malignant C-cell carcinoma combined
Thyroids - Benign follicular cell adenoma
Thyroids - Malignant follicular cell carcinoma
Thyroids - Benign follicular cell adenoma and malignant follicular cell carcinoma combined
Uterus - Benign endometrial polyp
Uterus - Malignant endometrial stromal sarcoma
Uterus - Malignant schwannoma
Uterus - Malignant adenocarcinoma
Uterus - Benign endometrial adenoma and malignant adenocarcinoma combined
Haematopoietic Tumour - Malignant large granular cell lymphoma
Haematopoietic Tumour - Malignant histiocytic sarcoma
Haematopoietic Tumour - Malignant mixed lymphoma

**Appears This Way
On Original**

Reference

Cox D. R. (1972). "Regression models and life tables," *Journal of the Royal Statistical Society B*, **34**, 187-220.

Fairweather, W.R., A. Bhattacharyya, P.P. Ceuppens, G. Heimann, L.A. Hothorn, R.L. Kodell, K.K. Lin, H. Mager, B.J. Middleton, W. Slob, K.A. Stallard, J. Ventre, and J. Wright (1998), "Biostatistical Methodology in Carcinogenicity Studies," *Drug Information Journal*, **32**, 401-421.

Gehan. (1965). "A generalized Wilcoxon test for comparing arbitrarily singly censored samples," *Biometrika* **52**, 203-223.

Hoel, D., and H. Walburg (1971), "Statistical analysis of Survival Experiments," *Journal of National Cancer Institute*, **49**, 361-372.

Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf (1980). "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments," Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426.

Thomas, Donald G., Breslow Norman, and Gart, John J. (1977). "Trend and Homogeneity analyses of Proportions and life Tale Data," *Computers and Biomedical Research* **10**, 373-381.

U.S. Department of Health and Human services (2001). "Guidance for Industry: Statistical Aspects of the Design, Analysis and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals," Center for Drug Evaluation and Research (CDER), Food and Drug Administration.

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

/s/

Ling Chen
1/8/2008 11:46:15 AM
BIOMETRICS

Karl Lin
1/8/2008 02:43:51 PM
BIOMETRICS
Concur with review



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Serial Number: 21-775 / 000

Drug Name: Entereg (Alvimopan) 12 mg capsule

Indication(s): Acceleration of gastrointestinal (GI) recovery following abdominal surgery

Applicant: Adolor Corp.

Date(s): Letter Date: May 9, 2006 PDUFA Date: November 9, 2006

Review Priority: I Standard

Biometrics Division: Division of Biometrics 3

Statistical Reviewer: Sonia Castillo, Ph.D.

Biometrics Team Leader: Stella Grosser, Ph.D.

Medical Division: Division of Gastroenterology Products

Clinical Team: Eric Brodsky, M.D., Clinical Reviewer
Ruyi He, M.D., Team Leader

Project Manager: Tanya Clayton

Key Words: Clinical studies, NDA review

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BACKGROUND	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	4
3.1 EVALUATION OF EFFICACY	4
3.1.1 <i>Overall Descriptive Statistics</i>	5
3.1.2 <i>Study 14CL314 Results</i>	5
3.2 EVALUATION OF SAFETY	6
4. FINDINGS IN SUBGROUP POPULATIONS	6
5. CONCLUSIONS.....	6

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant has provided evidence demonstrating the efficacy of ENTEREG (alvimopan) 12 mg for recovery of upper and lower gastrointestinal function in subjects following partial large or small bowel resection surgery with primary anastomosis.

1.2 Background

This submission is a complete response to the deficiencies outlined in the July 21, 2005 approvable action letter. The action letter outlined the efficacy information the Division requested and stated that:

[You have provided] insufficient proof of efficacy to support your proposed indication of acceleration of time to recovery of gastrointestinal function following bowel resection surgery. In Study 14CL302, the 6 mg alvimopan dose, but not the 12 mg dose, was statistically superior to placebo treatment in time to recovery of gastrointestinal motility as measured by GI3. In contrast, the 12 mg alvimopan dose in Study 14CL313 was statistically superior to placebo treatment while the 6 mg dose was not. Two additional studies (14CL308 and SB767905/001) failed to show statistical superiority for either dose compared to placebo treatment. When both doses are considered together, time to gastrointestinal recovery when assessed at 108 hours post-surgery ranged from one hour longer to 17 hours shorter relative to placebo treatment.

• The following [is] our recommendation for resolution of your above cited deficiency:

1. Provide at least one additional adequate and well-controlled study (in patients scheduled to have partial small or partial large bowel resection) that demonstrates statistically significant superiority of the proposed dosing regimen relative to placebo treatment. Your ongoing Study 14CL314 could address this deficiency if statistically superior results for the 12 mg alvimopan dose relative to placebo treatment are demonstrated.

In response, the Applicant has submitted one randomized, double-blind, placebo-controlled, parallel group study (14CL314) to evaluate the efficacy and safety of ENTEREG (alvimopan) 12 mg in the management of postoperative ileus (POI). According to the Applicant:

... Postoperative ileus (POI), the transient cessation of intestinal motility that occurs after abdominal or pelvic surgery, represents a significant clinical dilemma and is frequently the cause of delayed recovery and postoperative morbidity ...

During the early postoperative period, the signs and symptoms of POI correlate with absence of gastrointestinal motility and include abdominal distention and bloating; persistent abdominal pain; nausea, vomiting, or both; variable reduction of bowel sounds; delayed passage of or inability to pass flatus or stool; and inability to tolerate solid food. ...

POI is resolved when there is recovery of both upper and lower gastrointestinal (GI) function. From a clinical perspective, this occurs with the return of the subject's ability to tolerate solid food (upper GI recovery) and pass either flatus or a bowel movement (lower GI recovery).

The Applicant's proposed indication for the 12 mg dose of ENTEREG (alvimopan) is:

ENTEREG is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

1.3 Statistical Issues and Findings

There are no statistical issues in this submission. The result for the primary efficacy endpoint of "Recovery of GI Function (GI²)" is as follows:

The hazard ratio of 1.53 for the 12 mg dose of alvimopan compared to placebo (p-value<0.001) demonstrates evidence of efficacy for the 12 mg dose of alvimopan for use in the recovery of upper and lower GI function in patients following partial large or small bowel resection surgery with primary anastomosis.

2. INTRODUCTION

2.1 Overview

The Applicant has submitted one efficacy clinical study (14CL314) in adult subjects undergoing partial small or large bowel resection (BR) with primary anastomosis. This study is designed to assess the efficacy of 12 mg alvimopan in the management of postoperative ileus (POI) by accelerating the recovery of gastrointestinal (GI) function compared to placebo. Table 2.1 presents a brief summary of the study addressed in this review.

Table 2.1
Brief Summary of Clinical Study for Entereg

Study Number (No. of Centers / Country) and Dates of Study Conduct	Subject Population	Treatment	Number Randomized (MITT ¹)	Design ²
14CL314 (55 / U.S.) 6-9-04 to 12-20-05	Men and women undergoing partial small or large bowel resection with primary anastomosis, at least 18 yrs. of age	Alvimopan 12 mg bid Placebo Total	329 (317) 325 (312) 654 (424)	DB, R, PC, PG, MC

Source: Statistical Reviewer's listing.

¹ MITT = Modified Intent to Treat

² DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

This study was designed to evaluate the efficacy and safety of an earlier time period for the preoperative dose: 30 to 90 minutes before the scheduled start of surgery rather than at least than 2 hours before the scheduled start of surgery, as used in four earlier Phase 3 efficacy studies. Also, in contrast to the previous four efficacy studies, the primary efficacy measure in this study was a 2-component measure of GI recovery rather than a 3-component measure of GI recovery.

The Applicant's proposed indication for the 12 mg dose of ENTEREG (alvimopan) is:

ENTEREG is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

My review presents the Applicant's primary efficacy analyses for time to recovery of gastrointestinal (GI) function in detail and briefly presents the results for two clinically relevant secondary efficacy analyses.

2.2 Data Sources

The study reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items were located in the Electronic Document Room at \\Cdsub1\N21775\N_000 under submission date 5-9-2006.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Randomization was stratified by sex with subjects being randomized in a 1:1 ratio to receive alvimopan 12 mg (as two 6 mg alvimopan capsules) or identical placebo by mouth, given 30 to 90 minutes before the scheduled start of surgery and then twice daily until hospital discharge or for a maximum of 7 days of postoperative treatment. The study duration was defined as 10 postoperative days plus the day of surgery starting from end of the surgery (i.e., $10 \times 24 + 24 = 264$ hours).

After surgery, a subject's gastrointestinal function was assessed twice daily, at the morning and afternoon assessments, by the study coordinator until hospital discharge or for a maximum of 10 postoperative days while the subject was hospitalized. Subjects were questioned regarding the occurrence of flatus or bowel movements (BM) and the tolerability of solid food. In addition, the surgeon evaluated the subject's readiness for hospital discharge based upon their definition of recovery of GI function twice daily, at the morning and afternoon assessments.

The primary objective of this study is to demonstrate that alvimopan 12 mg administered 30 to 90 minutes before the scheduled start of surgery and then twice daily (BID) until hospital discharge (or for a maximum of 7 days of postoperative treatment) accelerates recovery of GI function in subjects undergoing partial small or large bowel resection compared to placebo. The protocol does not propose a clinically meaningful threshold value to demonstrate success.

The primary efficacy endpoint is the time (hours) to recovery of GI function after end of surgery, as measured by a 2-component composite endpoint (GI²) representing full (upper and lower) GI function recovery. GI² is defined as: *maximum [time to first bowel movement, time to first solid food]*. In addition, according to the Clinical Reviewer, two important secondary time-to-event endpoints are 1) time to ready for hospital discharge based solely on GI recovery as defined by the surgeon and 2) time to hospital discharge order written.

The null hypothesis is there is no difference between the alvimopan 12 mg group and placebo group in the time to recovery of GI function. The primary analysis of treatment effect on time to recovery of GI function uses a Cox proportional hazard model that includes the main effect of treatment. Time to an event was defined as the duration, in hours, from the end of surgery (last suture or staple) to the time of the first event. The p-values for comparisons between alvimopan 12 mg vs. placebo are calculated using the Wald Chi-square test, 2-sided at the 0.05 α -level. Hazard ratios and their 95% confidence intervals are presented. Quartiles (25th, 50th (median), and 75th percentiles) for the time to recovery of GI function (GI²) are also estimated, based on the Kaplan-Meier (KM) survival curve. In addition, analyses similar to the primary efficacy endpoint comparing alvimopan 12 mg to placebo are presented for the two important secondary time-to-event efficacy endpoints.

The protocol-specified modified intent to treat (MITT) population is the main efficacy analysis population. The MITT population includes all randomized and treated subjects who received the protocol-specified surgery and have at least one post-surgical efficacy evaluation for bowel movement or toleration of solid food.

This review presents the results of the protocol-specified primary efficacy analyses and briefly presents the results of the two important secondary efficacy analyses.

3.1.1 Overall Descriptive Statistics

Demographic and baseline characteristics are comparable between the treatment groups. The subjects' mean age was 59.9 years for alvimopan 12 mg and 59.6 years for placebo. In both groups, the majority of subjects are Caucasian (>82%) and have similar proportions of each gender (about 50%).

Table 3.1 presents the number of randomized subjects and their disposition. Treatment discontinuation is 18.8 % in the alvimopan 12 mg group and 22.2% in the placebo group, with the primary reason being adverse events. Of the patients who stop treatment, discontinuation due to adverse events is 51.6% in the alvimopan 12 mg group and 62.5% in the placebo group.

Table 3.1
Summary of Subject Disposition for Study 14CL314

	Alvimopan 12 mg	Placebo
Randomized (ITT)	329	325
Modified Intent to Treat (MITT)*	317 (96.4)	312 (96.0)
Completed Treatment*	267 (81.2)	253 (77.8)
Discontinued Treatment* n (%)	62 (18.8)	72 (22.2)
Discontinued Due to Adverse Events** n (%)	32 (51.6)	45 (62.5)
Administrative	0 (0)	1 (1.4)
Subject Declined Further Study Medication Dosing	8 (12.9)	7 (9.7)
Protocol Violation	20 (32.3)	18 (25.0)
Other	2 (3.2)	1 (1.4)

Source: Table 4, page 56, Study 14CL314 report.

* With respect to number of ITT subjects.

** With respect to number of all discontinuations.

3.1.2 Study 14CL314 Results

The Applicant's results for the primary efficacy endpoint and two important secondary endpoints are presented in Table 3.2. This reviewer concurs with the Applicant's results. The primary time-to-event efficacy endpoint of GI² (recovery of GI function) demonstrated a significant hazard ratio of 1.53 for alvimopan 12 mg compared to placebo (p<0.001).

Results for the two important secondary time-to-event endpoints are as follow:

- “Ready for hospital discharge” demonstrated a significant hazard ratio of 1.38 for alvimopan 12 mg compared to placebo (p< 0.01)
- “Hospital discharge order written” demonstrated a significant hazard ratio of 1.40 for alvimopan 12 mg compared to placebo (p<0.001)

Table 3.2
Study 14CL314: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written

Time-to-event Endpoint	N	Censored n (%)	Quartile (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value	
Recovery of GI Function (GI²)						
Placebo	312	44 (14.1)	25%	73.5 (71.1, 76.3)	1.53 (1.29, 1.82)	<0.001*
			50%	96.6 (93.7, 101.2)		
			75%	131.2 (124.0, 142.1)		
Alvimopan 12 mg	317	38 (12.0)	25%	64.3 (61.0, 68.6)		
			50%	80.0 (76.7, 88.0)		
			75%	110.9 (102.3, 117.6)		
Ready for Hospital Discharge						
Placebo	312	30 (9.6)	25%	70.2 (67.7, 72.3)	1.38 (1.17, 1.63)	<0.001*
			50%	91.3 (88.2, 94.0)		
			75%	123.0 (116.3, 137.8)		
Alvimopan 12 mg	317	22 (6.9)	25%	67.0 (65.8, 69.6)		
			50%	80.7 (77.6, 89.1)		
			75%	101.9 (97.5, 113.6)		
Hospital Discharge Order Written						
Placebo	312	27 (8.7)	25%	95.2 (93.0, 96.9)	1.40 (1.19, 1.65)	<0.001*
			50%	119.9 (117.5, 134.4)		
			75%	166.2 (156.1, 170.5)		
Alvimopan 12 mg	317	14 (4.4)	25%	90.3 (88.7, 92.9)		
			50%	112.1 (101.9, 115.5)		
			75%	141.1 (132.5, 143.7)		

Source: Tables 11, 12, and 15; pages 70, 74, and 83; Study 14CL314 report.

^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.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

There are no subgroup populations of interest in this submission.

5. CONCLUSIONS

Study 14CL314 demonstrates statistically significant results for the 12 mg dose of alvimopan. This result provides evidence of efficacy for the 12 mg dose of alvimopan for use in the recovery of upper and lower gastrointestinal function in subjects following partial large or small bowel resection surgery with primary anastomosis.

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

/s/

Sonia Castillo
10/26/2006 11:37:51 AM
BIOMETRICS

Stella Grosser
11/1/2006 10:06:25 AM
BIOMETRICS

M E M O R A N D O M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS
DIVISION OF BIOMETRICS VI**

DATE: September 15, 2006

FROM: Yu-te Wu, Ph.D., Mathematical Statistician
Quantitative Safety and Epidemiology Team
Division of Biometrics VI

THROUGH: George Rochester, Ph.D., Lead Mathematical Statistician
Quantitative Safety and Epidemiology Team
Division of Biometrics VI

Yi Tsong, Ph.D., Deputy Director
Division of Biometrics VI

Stella Machado, Ph.D., Director
Division of Biometrics VI

TO: Brian Harvey, M.D., Ph.D. Director
Division of Gastrointestinal Products

Cynthia Kornegay, Ph.D. Epidemiologist
Division of Drug Risk Evaluation

Tanya Clayton, Project Manager
Division of Gastrointestinal Products

SUBJECT: Review of the briefing document entitled, "GlaxoSmithKline Safety Board Recommendations to Continue Alvimopan Clinical Development Program to Treat OBD Following Safety Review of Myocardial Infarction and Related Events". Document submitted to NDA 21-775 on August 1, 2006. The Quantitative Safety and Pharmacoepidemiology Team was asked to provide comment on three questions.

Background:

Alvimopan (Entereg) capsules is an investigational opioid antagonist. In a 12 month safety study (Study 014) eight serious cardiovascular events (7 myocardial infarctions and 1 unstable angina) were observed in patients treated in the Alvimopan group compared to zero event in the placebo group. This is the only study in the development program specifically designed for safety although four other studies designed primarily to

demonstrate efficacy also collected safety data. The finding in this study is of concern especially since this was not previously observed in the short-term (3 – 12 weeks in duration). Study 014 is a randomized, double-blind, placebo-controlled, multi-center Phase III study to evaluate the long-term safety for the treatment of opioid-induced bowel dysfunction (OBD) in adults taking opioid therapy for persistent non-cancer pain and is not yet complete at the time this report is received. Study 014 is designed to evaluate the clinical adverse events. The safety assessments include adverse event reporting, pain intensity ratings, opioid consumption, vital signs, chemistry and hematology. There is no prior evidence to suggest that exposure to Alvimopan may increase the risk of cardiovascular events. The safety monitoring board recommended that the trial continue despite the above finding.

The GSK global safety board (GSB) concluded that while it was concerned about the CV imbalance of events in Study 014:

- The differences in rates of myocardial infarctions (MIs) and related serious adverse events in Study 014 compared to Studies 012 and 013 remained unexplained
- The imbalance of events observed on alvimopan vs. placebo in Study 014 was not supported by the incidence of events in all GSK OBD studies
- The increased number of total serious adverse events (SAEs) of myocardial infarction and related events in Study 014 could be due to a chance allocation

The Office of Drug Safety requested our consultation on the statistical method conducted in this report.

Appropriateness of the pooled analysis

Of the OBD studies, the objective of Study 014 is to evaluate the long-term safety of Alvimopan for 12 months, whereas the objectives of other studies are to evaluate the efficacy and safety of Alvimopan for relatively short treatment durations (3-12 weeks). The study designs are summarized in the table below. Because of differences in objectives, the underlying conditions of study design, conduct and population for Study 014, this study is likely to be substantially different from other studies, despite Sponsor's Table 10 (page 33) suggesting that the overall demographics are not different between studies 8, 11, 12, 13 and 14.

Table 1: List of Randomized, Double-blind, Placebo-controlled, Multi-center Phase 2b/Phase 3 Clinical Studies

Study number (Status)	Design	Objective
8 (ongoing)	Phase 2b, 3-6 weeks	Efficacy & safety Cancer patients
11 (completed)	Phase 2b, 6 weeks	Efficacy & safety Non-cancer patients
12,13 (ongoing)	Phase 3, 12 weeks	Efficacy & safety Non-cancer patients
14 (ongoing)	Phase 3, 12 months	Long-term safety Non-cancer patients

Source: Appendix 9.1, Sponsor submission of 8/1/06

Many issues need to be considered prior to performing a pooled analysis. See Section VI D and E of the *FDA Guidance for Industry: Premarketing risk assessment* (March 2005). The safety signal in Study 014 remains of concern, and the reduced association by the pooled analysis needs to be carefully examined. Sensitivity analyses are important to understand the robustness of any pooling strategy, if pooling is considered appropriate. Sponsor is required to provide principles used when pooling data and provide sensitivity analyses.

Statistical analysis in Study 014

The significance level of increased cardiovascular risk (number of events/estimated patient years) in the Alvimopan group compared to the placebo group is 0.06 based on the exact test. The 95% confidence interval of incidence density risk (IDR) does not include one based on the Mid-p' corrected method (Lancaster, 1961; Miettinen 1985; Pratt and Gibbons, 1981), a less conservative approach, which we prefer in the safety analysis. The number of patient years in Study 014 is extrapolated based on information provided in sponsor's Table 7 (page 28). The overall incidence rate per 100 patient-years in the combined group is 4.3. Given that the total number of observed CV cases is 8, one can estimate the total number of patient-years as $8/0.043 = 186.05$. In the Alvimopan group, the incidence rate is 6.4 per 100 patient-years. Given that eight cases are from the Alvimopan group, the estimated patient-years in the Alvimopan group is $8/0.064 = 125$. Therefore, the estimated patient-years in the placebo group is 61.05.

Table 2: Comparison of Incidence rate of Myocardial Events between Alvimopan and Placebo groups in Study 014

Alvimopan (number of events/estimated patient-years)	Placebo (number of events/estimated patient- years)	P-value (testing IDR =1)	Exact 2-sided 95% CI
8/125	0/61.05	1-sided exact test 0.042	Exact (0.83, +∞)
		2-sided exact test 0.06	Mid-p corrected (1.08, +∞)

* Computation performed using StatXact 7 PROCs.

Meta-analysis

If the sponsor decides to perform a meta-analysis to adjust for the between-study variability, please provide justification for any pooled analyses.

Cardiovascular risk remains a potential safety signal for patients taking Alvimopan. The pooled analysis performed by the sponsor does not rule out this possibility.

The following additional data and analyses are requested.

- Provide the patient-years data in the Alvimopan and placebo groups for studies 8, 11, 12, 13 & 14.
- Provide the time-to-cardiovascular event data (MI and unstable angina) in the Alvimopan and placebo groups for studies 8, 11, 12, 13 & 14.
- For studies 8, 11, 12, 13 & 14, calculate the incidence rate per 100 patient years and the incidence density risk for MI alone and with unstable angina of Alvimopan and placebo groups with exact 95% confidence interval.

Thank you for asking us to comment on this report. If you need further assistance please do not hesitate to contact us at (301) 796-0986.

References:

Lancaster HO (1961). Significance tests in discrete distributions. *Journal of the American Statistical Association* 56; 223-234.

Miettinen OS (1985). *Theoretical Epidemiology: Principles of Occurrence Research in Medicine*. John Wiley & Sons, New York.

Pratt JW, Gibbons JD (1981). *Concepts of Nonparametric Theory*. Springer-Verlag, New York.

Reviewer:

Yu-te Wu, Ph.D.
Mathematical Statistician
DB VI/OB/OTS/CDER

Concurring Reviewer:

George Rochester, Ph.D., RAC
Lead Mathematical Statistician - Safety
DB VI/OB/OTS/CDER

Concurring Reviewer:

Yi Tsong, Ph.D., Deputy Director
DB VI/OB/OTS/CDER

Concur :

Stella Machado, Ph.D., Director
DB VI/OB/OTS/CDER

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

/s/

Yu-Te Wu
9/15/2006 05:20:08 PM
BIOMETRICS

Yi Tsong
9/15/2006 05:23:19 PM
BIOMETRICS

George Rochester
9/15/2006 05:29:20 PM
BIOMETRICS

Statistical Consultation – Statistical Analysis Plan Assessment

NDA #: 21-775 (Serial 000)
Applicant: Adolor Corp.
Name of Drug: Entereg (alvimopan) Capsules
Indication: Acceleration of gastrointestinal (GI) recovery following abdominal surgery
Documents Reviewed: Statistical Analysis Plan for Protocol 14CL314: A Phase 3b, Multicenter, Double-Blind, Placebo-Controlled, Parallel Study of Alvimopan for the Management of Postoperative Ileus
Date received: 10 / 14 / 2005
Medical Reviewer: Eric Brodsky, M.D.
Statistical Reviewer: Sonia Castillo, Ph.D.

This submission contains the revised statistical analysis plan (SAP) for ongoing Study 14CL314, a Phase 3, multicenter, double-blind, placebo-controlled, parallel group study of alvimopan 12 mg for the management of postoperative ileus (POI). This revised SAP contains three new endpoints (two of which are used to create the third which is a new secondary endpoint) and changes to the analysis methods. The new endpoints and their definitions are presented in the following table.

Endpoint	Definition
Postoperative Nasogastric Tube (NGT) insertion	Regardless of whether an NGT was used preoperatively or not, when inserted postoperatively as an intervention for an acute event, the subject is considered to have had an event of postoperative NGT insertion.
Complications of Postoperative Ileus (POI)	A subject is considered to have an event of complications of POI if the subject had any of the following serious adverse events resulting in prolonged hospital stay or readmission \leq 30 days of the initial hospital discharge: nausea, vomiting, constipation, abdominal distension / bloating, postoperative ileus, paralytic ileus, complicated ileus, adynamic ileus, early postoperative small bowel obstruction (EPSBO – a small bowel obstruction with an onset date \leq 30 days from the date of surgery). These events must be identified by the verbatim term of the SAE before breaking the blind.
Postoperative Morbidity (POM)	Postoperative morbidity includes subjects who had either postoperative NGT insertion or complications of POI.

Source: Statistical Reviewer's listing.

The null hypothesis before this submission was that there is no difference between alvimopan 12 mg and placebo in GI^2 . The revised null hypothesis is that there is no difference between alvimopan 12 mg and placebo on each efficacy endpoint (GI^2 , DOW, and POM). The Sponsor proposes a hierarchical method to test the revised hypothesis with the order of the being hierarchy one primary endpoint (GI^2) and two secondary endpoints (DOW and POM), in that order. The following will be presented to describe the magnitude of treatment benefit based on GI^2 and DOW: Kaplan-Meier (KM) estimates at 25th, 50th (median) and 75th percentiles and difference in median, KM means and difference in KM means and its 95% confidence interval, a responder analysis providing the number and percent of subjects who achieved an event for each postoperative day (PSD) period starting from PSD 0 with censored subjects during a PSD period included in the denominator.

Also, the number of secondary efficacy endpoints has been reduced from 13 to two, which are time to hospital discharge order written (DOW) and proportion of subjects with postoperative morbidity (POM). The other 11 secondary efficacy endpoints are either labeled as "Other Endpoints" or have been dropped from efficacy analysis.

Statistical Reviewer's Comments for the Sponsor:

(These statistical comments have been sent by the Division to the Sponsor and need not be conveyed.)

1. Please provide the rationale for choosing a hierarchical testing strategy.
2. Please clarify why patients were stratified by gender when they were randomized.

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

/s/

Sonia Castillo
12/19/2005 03:24:52 PM
BIOMETRICS

07/07/05

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

NDA/Serial Number: 21-775 / 000
Drug Name: Entereg (Alvimopan) 12 mg capsule
Indication(s): Acceleration of gastrointestinal (GI) recovery following abdominal or pelvic surgery
Applicant: Adolor Corp.
Date(s): Letter Date: June 25, 2004 PDUFA Date: July 25, 2005
Review Priority: 1 Standard
Biometrics Division: Division of Biometrics 2, HFD-715
Statistical Reviewer: Sonia Castillo, Ph.D.
Biometrics Team Leader: Stella Grosser, Ph.D.
Medical Division: Division of Gastrointestinal and Anti-Coagulant Drug Products, HFD-180
Clinical Team: Eric Brodsky, M.D., Clinical Reviewer
Ruyi He, M.D., Team Leader
Project Manager: Melissa Furness

An error was made in reporting the value of the hazard ratio for the time-to-event endpoint "Ready for Hospital Discharge" in Table 3.9 on page 12 of the statistical review. The value should be 1.11 not 1.54 as listed. Table 3.9 should be replaced with the one shown below.

Table 3.9
Study SB767905/001: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
Placebo	229	19 (8)	81.3 (65.8, 115.3)		
Alvimopan 6 mg	237	18 (8)	74.6 (58.8, 97.1)	1.22 (1.01, 1.47)	0.042
Alvimopan 12 mg	238	19 (8)	76.9 (62.4, 101.2)	1.13 (0.94, 1.37)	0.200
Ready for Hospital Discharge					
Placebo	229	29 (13)	137.5 (99.8, 173.4)		
Alvimopan 6 mg	237	30 (13)	125.3 (94.0, 165.0)	1.16 (0.96, 1.41)	0.134
Alvimopan 12 mg	238	28 (12)	127.2 (94.5, 166.9)	1.11 (0.92, 1.35)	0.287
Hospital Discharge Order Written					
Placebo	229	33 (14)	192.8 (161.3, 266.3)		
Alvimopan 6 mg	237	37 (16)	191.5 (158.6, 261.1)	1.08 (0.88, 1.31)	0.471
Alvimopan 12 mg	238	35 (15)	191.5 (158.6, 261.5)	1.07 (0.88, 1.30)	0.493

Source: Tables 4 and 5, pages 10 and 13, Study SB767905/001 Study Report.

^a Estimate (in hours) was calculated from a Cox proportional hazards model that included treatment only for bowel resection subjects only and confidence limits are the lower and upper quartiles.

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

^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.

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

/s/

Sonia Castillo
7/7/05 02:41:20 PM
BIOMETRICS

Stella Grosser
7/7/05 04:02:10 PM
BIOMETRICS

07/01/05



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Serial Number: 21-775 / 000

Drug Name: Entereg (Alvimopan) 12 mg capsule

Indication(s): Acceleration of gastrointestinal (GI) recovery following abdominal or pelvic surgery

Applicant: Adolor Corp.

Date(s): Letter Date: June 25, 2004 PDUFA Date: July 25, 2005

Review Priority: 1 Standard

Biometrics Division: Division of Biometrics 2, HFD-715

Statistical Reviewer: Sonia Castillo, Ph.D.

Biometrics Team Leader: Stella Grosser, Ph.D.

Medical Division: Division of Gastrointestinal and Anti-Coagulant Drug Products, HFD-180

Clinical Team: Eric Brodsky, M.D., Clinical Reviewer
Ruyi He, M.D., Team Leader

Project Manager: Melissa Furness

Key Words: Clinical studies, NDA review

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BACKGROUND.....	3
1.3 STATISTICAL ISSUES AND FINDINGS.....	3
2. INTRODUCTION	4
2.1 OVERVIEW.....	4
2.2 DATA SOURCES.....	5
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY.....	5
3.1.1 Overall Study Descriptive Information	7
3.1.2 Study 14CL302 Results.....	8
3.1.3 Study 14CL308 Results.....	9
3.1.4 Study 14CL313 Results.....	11
3.1.5 Study SB767905/001 Results.....	12
3.1.6 Additional Analyses.....	13
3.2 EVALUATION OF SAFETY	13
4. FINDINGS IN SUBGROUP POPULATIONS	13
4.1 GENDER, RACE, AND AGE	13
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	13
5. CONCLUSIONS.....	14
APPENDIX 1	15
APPENDIX 2.....	17

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The four submitted studies do not provide clear evidence demonstrating the efficacy of either the 6 mg dose or the 12 mg dose of ENTEREG (alvimopan), in terms of recovery of GI function, in bowel resection subjects.

1.2 Background

The Sponsor has submitted four randomized, double-blind, placebo-controlled, parallel group studies to evaluate the efficacy and safety of ENTEREG (alvimopan) in the management of postoperative ileus (POI). According to the Sponsor,

... [POI] is characterized by a transient cessation of bowel function with a variable reduction in motility sufficient to prevent effective transit of intestinal contents. Patients undergoing major abdominal surgery are at highest risk for developing POI ... Signs and symptoms of POI correlate with lack of normal GI function and may include ... delayed passage of or inability to pass flatus or stool; and inability to tolerate a solid diet.

Multiple factors are thought to contribute to the pathogenesis of POI. Several major pathways have been identified: (1) neurogenic (surgical stress response stimulates inhibitory neural reflexes resulting in decreased bowel motility); (2) inflammatory (bowel manipulation/resection stimulates resident macrophage and neutrophil recruitment with release of inflammatory mediators that reduce bowel motility, this includes endogenous opioid peptides); (3) hormonal (surgical stress results in elevation of corticotrophin-releasing factor, which stimulates release of inflammatory mediators in the bowel); and (4) pharmacologic (primarily exogenous opioids, eg., morphine, binding to μ -receptors in the GI tract which results in disorganized and non-propulsive motility and, thus, prolongs ileus). ...

The duration of ileus after surgery varies throughout the GI tract with return of colonic function ... usually being rate-limiting to full GI recovery. ... Recovery of both upper and lower GI function represents resolution of POI. Clinically, this correlates with the patient's ability to tolerate solid food (upper GI recovery) and pass either flatus or a BM (lower GI recovery).

The Sponsor's proposed indication for the 12 mg dose of ENTEREG (alvimopan) in bowel resection and hysterectomy subjects is:

ENTEREG is indicated to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery.

In addition, there is one ongoing U.S. Phase 3 study in bowel resection patients comparing 12 mg alvimopan to placebo using a 2-component composite endpoint representing complete GI recovery (GI2). This study's expected completion date is late 2006.

1.3 Statistical Issues and Findings

There are two statistical issues in this submission. They are the use of the mean time-to-event to describe the magnitude of treatment effect and estimation of the median time-to-event using the Cox proportional hazards model.

I will not present the estimate of mean time-to-event to describe the magnitude of treatment effect because the mean is biased in the presence of censoring and the inherent skewness of time-to-event data. Also, the Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format states in Section III.D.3. that, "When time-to-event endpoints (e.g., mortality) are used, median or mean survival alone is not usually an adequate descriptor. Survival curves (or event-free survival curves) and hazard ratios are often effective ways to display such data." The Sponsor's rationale for using the mean time-to-event to describe the magnitude of treatment effect, given on page 4 of the April 21, 2005 submission, is as follows:

... although the hazard ratios being greater than 1 indicate that the event has occurred faster (earlier) in the alvimopan treatment groups, this clinical benefit cannot be translated directly into how much faster (earlier), i.e. the magnitude of treatment effect or clinical benefit.

While the Cox proportional hazards model estimate of median time-to-event is not inappropriate in the situation where there are no covariates specified in the model, I also present the Kaplan-Meier estimate of the median time-to-event.

Furthermore, the Clinical Reviewer requested that analyses be performed by individual surgery subgroup, i.e. bowel resection or hysterectomy, to determine efficacy in each group. Section 3.1 lists the clinical reasons for performing the subgroup analyses. These subgroup analyses did not demonstrate efficacy in the hysterectomy subgroup. The efficacy results for the bowel resection subgroup is described next.

The following are the results for the primary efficacy endpoint of “Recovery of GI Function (GI³)” in bowel resection patients for the four studies:

- Study 14CL302 demonstrates a significant hazard ratio of 1.48 for the 6 mg dose of alvimopan compared to placebo (p-value=0.009)
- Study 14CL313 demonstrates a significant hazard ratio of 1.49 for the 12 mg dose of alvimopan compared to placebo (p-value=0.002)
- Studies 14CL308 and SB767905/001 do not demonstrate significant hazard ratios for either alvimopan dose compared to placebo

These results do not show consistent evidence of efficacy for either the 6 mg or 12 mg dose of alvimopan for use in the recovery of GI function in bowel resection patients.

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted four efficacy clinical studies in adult subjects undergoing partial small or large bowel resection (BR) with primary anastomosis or simple or radical total abdominal hysterectomy (sTAH or rTAH). These studies are designed to assess the efficacy of two doses (6 mg and 12 mg) of alvimopan in the management of postoperative ileus (POI) by accelerating the recovery of gastrointestinal (GI) function compared to placebo. Table 2.1 presents a brief summary of each of the four studies addressed in this review.

In addition, the Sponsor has submitted one large safety and tolerability study in subjects undergoing total abdominal simple hysterectomy (study 14CL306, N=519 enrolled subjects). This study is relevant because efficacy, using the same primary endpoint as in the three efficacy studies, was not demonstrated in this group of patients. Further rationale for examining this study in this review will be addressed in Section 3.1 below.

Table 2.1
Brief Summary of Clinical Studies for Entereg

Study Number (No. of Centers / Country) and Dates of Study Conduct	Subject Population	Treatment	Number Randomized (MITT ¹)	Design ²
14CL302 (40 / U.S.) 3-8-01 to 12-16-02	Men and women undergoing large bowel resection, radical total abdominal hysterectomy, or simple total abdominal hysterectomy, 18 to 80 yrs. of age	Alvimopan 6 mg bid Alvimopan 12 mg bid Placebo Total	152 (141) 146 (138) 153 (145) 451 (424)	DB, R, PC, PG, MC
14CL308 (37 / U.S.) 12-19-01 to 11-3-03	Men and women undergoing a partial small or large bowel resection with primary anastomosis, radical total abdominal hysterectomy, or simple total abdominal hysterectomy, at least 18 yrs. of age	Alvimopan 6 mg bid Alvimopan 12 mg bid Placebo Total	220 (204) 222 (204) 224 (207) 666 (615)	DB, R, PC, PG, MC
14CL313 (30 / U.S., 4 / Canada) 1-20-02 to 6-4-03	Men and women undergoing a partial small or large bowel resection with primary anastomosis or radical total abdominal hysterectomy, at least 18 yrs. of age	Alvimopan 6 mg bid Alvimopan 12 mg bid Placebo Total	169 (155) 176 (165) 165 (149) 510 (469)	DB, R, PC, PG, MC
SB767905/001 (70/Europe, 5/Australia, 5/ New Zealand) 4-28-03 to 10-7-04	Men and women undergoing a partial small or large bowel resection with primary anastomosis, at least 18 yrs. of age	Alvimopan 6 mg bid Alvimopan 12 mg bid Placebo Total	248 (237) 251 (239) 242 (229) 741 (705)	DB, R, PC, PG, MC

Source: Statistical Reviewer's listing.

¹ MITT = Modified Intent to Treat

² DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

The Sponsor's proposed indication is:

ENTEREG is indicated to accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery.

My review presents the Sponsor's protocol-specified primary efficacy analyses for time to recovery of gastrointestinal (GI) function in detail and briefly presents two clinically relevant secondary efficacy analyses. Additional efficacy analyses requested by the Clinical Reviewer are also presented.

2.2 Data Sources

The study reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items were located in the Electronic Document Room at \\Cdsub1\N21775\N_000 under various submission dates ranging from 6-25-2004 to 4-21-2005.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

In all studies, except Studies 14CL313 and SB767905/001, center and surgery type (BR, rTAH or sTAH) were stratification factors used for randomization of eligible subjects. Within these strata, subjects were randomized in a 1:1:1 ratio to receive alvimopan (6 mg or 12 mg) or identical placebo, given as 2 capsules at least 2 hours prior to the scheduled start of surgery and then twice daily until hospital discharge or for a maximum of 7 days of postoperative treatment. The dosing regimen either was two placebo capsules, one 6 mg alvimopan capsule and 1 placebo capsule, or two 6 mg alvimopan capsules. The study duration was defined as 10 postoperative days plus the day of surgery starting from end of the surgery (i.e., $10 \times 24 + 24 = 264$ hours).

The duration of surgery was recorded. After surgery, a subject's gastrointestinal function was assessed twice daily, at the morning and afternoon assessments, by the study coordinator until hospital discharge or for a maximum of 10 postoperative days while the subject was hospitalized. Subjects were questioned regarding the occurrence of flatus or bowel movements (BM) and the tolerability of solid food. In addition, the surgeon evaluated the subject's readiness for hospital discharge based upon their definition of recovery of GI function twice daily, at the morning and afternoon assessments.

The protocol-specified primary objective for studies 14CL302, 14CL308, 14CL313, and SB767905/001 is to demonstrate a statistically significant acceleration in time to recovery of GI function for two dose levels of alvimopan (6 mg and 12 mg) compared to placebo. The protocols do not propose a clinically meaningful threshold value to demonstrate success.

The primary efficacy endpoint is the time (hours) to recovery of GI function after end of surgery, a composite endpoint (GI³) representing full (upper and lower) GI function recovery. According to the Sponsor:

Recovery of both upper and lower GI function represent resolution of POI. Clinically, this correlates with the ability to tolerate solid food (upper GI recovery) and pass either flatus or a BM (lower GI recovery). These are standard and well-accepted clinical endpoints for evaluating return of bowel function after intra-abdominal surgery.

GI³ is defined as: *maximum [minimum (time to first flatus, time to first BM), time to first solid food]*. In addition, two important secondary time-to-event endpoints are 1) ready for hospital discharge based solely on the recovery of GI function as defined by the surgeon and 2) hospital discharge order written.

There are two null hypotheses: 1) there is no difference between the alvimopan 6 mg group and placebo group in the time to recovery of GI function, and 2) there is no difference between the alvimopan 12 mg group and placebo group in the time to recovery of GI function.

The primary analysis of treatment effect on time to recovery of GI function uses a Cox proportional hazard model that includes the main effect of treatment and is stratified by surgery type (BR/rTAH vs. sTAH). The Sponsor, assuming that BR and rTAH surgery durations are similar and that surgery duration correlates strongly with GI recovery, grouped the BR and rTAH subjects together for analysis.

The nominal p-values for comparisons between each alvimopan dose vs. placebo are calculated using the Wald Chi-square test. The Hochberg step-up method is used to control the overall Type I error at 5% or less. Hazard ratios and their 95% confidence intervals are presented. The magnitude of the treatment effect on the recovery of GI function is presented as the difference between the alvimopan and placebo arms in mean time-to-event (estimated by the area under the Kaplan-Meier survival curve), 95% CI of the difference in estimated means, and p-values for comparison of the differences in means.

The protocol-specified modified intent to treat (MITT) population is the main efficacy analysis population. The MITT population includes all treated subjects who received the protocol-specified surgeries and have at least one on-treatment evaluation of flatus, BM, or toleration of solid food post-surgery.

According to the Clinical Reviewer, the two most important secondary time-to-event efficacy endpoints are ready for hospital discharge based solely on surgeon's assessment of recovery of GI function and time to hospital discharge order written. According to the Clinical reviewer:

These endpoints demonstrate the ability of a treatment to reduce the length of hospitalization. Post op ileus (POI) is a serious disease because it prolongs the need for hospitalization. Thus, a response to these endpoints implies a reduction of a serious aspect of POI. The sooner a patient is able to go home, the greater the reduction of the chance of complications may occur like (blood clots in the legs from not getting out of bed; complications from intravenous catheters; complications from the use of non-oral nutrition). Furthermore, the sooner someone has improved GI tract motility then the sooner they can eat and they will be less likely to get poor nutrition (poor nutrition can be associated with poor wound healing or a weakened ability to fight an infection). They represent an improvement of the patient's condition - reducing the length of a hospital stay.

Comparisons, similar to the primary efficacy endpoint, of each alvimopan dose vs. placebo are presented by me.

There are two statistical issues in this submission. They are the protocol-specified use of the mean time-to-event and estimation of the median time-to-event using the Cox proportional hazards model.

I will not present the protocol-specified estimate of mean time-to-event because the mean is biased in the presence of censoring and the inherent skewness of time-to-event data. In addition to the protocol-specified Cox proportional hazards model estimate of median time-to-event, I also present the estimated median time-to-event from the Kaplan-Meier survival curve.

The Clinical Reviewer requested that analyses be performed by individual surgery subgroup, i.e. bowel resection or hysterectomy, to determine efficacy in each group. Following are the clinical reasons for the subgroup analyses requested by the Clinical Reviewer:

- 1) Study 14CL306 with 100% sTAH patients had no efficacy and Study 14CL313 with 96% BR patients initially appeared to have stronger evidence of efficacy. Thus, it appeared that the BR patients were driving efficacy.
- 2) Many textbooks about post op ileus (POI) have stated that the motility of the colon (large bowel), small bowel, and stomach recovers in 3 days, 1 day, and 1-2 days respectively, after surgery. Thus, the rate-limiting step in the recover of GI motility after surgery is the colon. Therefore, surgery on the large bowel (cutting into the large bowel) may have slower GI motility recovery compared to surgery on the uterus.
- 3) The rTAH/BR grouping was not logical. This was based on duration of surgery (rTAH surgeries seemed to have similar surgery durations as BR surgeries in their phase II studies). It would be more logical to group [by organ system]; rTAH and sTAH versus (small and large) bowel surgeries. In addition, there are other factors that determine the recovery of GI tract motility besides duration of surgery. The Sponsor selected only one factor (length of surgery).
- 4) Historically, it is known that bowel surgery patients have longer recovery times than other surgeries, similar to orthopedics or brain surgery. So different surgical types have influenced the recovery of GI tract motility. This supports the grouping of BR patients versus the hysterectomy patients.

This review presents the protocol-specified primary efficacy analyses and briefly presents the important secondary efficacy analyses.

3.1.1 Overall Study Descriptive Information

The following section presents demographic and baseline characteristics, subject disposition, and distribution of surgery types for each of the four submitted efficacy studies – 14CL302, 14CL308, 14CL313, and SB767905/001.

Demographic and baseline characteristics are comparable among the treatment groups within each study. The subjects' mean age ranges from 56.1 to 65.2 years for both alvimopan doses and from 56.7 to 64.2 years for placebo. The mean age ranges from 57 to 64.5 years across all studies. The majority of subjects are Caucasian (77 to 99%) across all studies and female (63 and 67%) for Studies 302 and 308, majority male (55%) for Study SB767905/001, and with similar proportions of each gender (50.8% female vs. 49.2% male) in Study 313.

Table 3.1 presents the number of randomized subjects and the disposition of the subjects for all four studies. Study discontinuation for each treatment group across all four studies ranges from 15% to 23.1 % in the alvimopan 6 mg group, 17.1% to 26.7% in the alvimopan 12 mg group, and 20.9% to 29.7% in the placebo group. The primary reason for study discontinuation across all studies for all treatment groups is adverse events, except for study SB767905/001. Discontinuations due to adverse events range from 41.7% to 66.7% for both alvimopan doses and from 57.1% to 68.8% for placebo. For study SB767905/001, the primary reason for study discontinuation is other reasons, which ranges from 46% to 51% for both alvimopan doses and is 45.5% for placebo.

Table 3.1
Summary of Subject Disposition for Studies 14CL302, 14CL308, 14CL313, and SB767905/001

	Alvimopan 6 mg	Alvimopan 12 mg	Placebo
Study 14CL302 (U.S.)			
Randomized (ITT)	152	146	153
Modified Intent to Treat (MITT)*	141 (92.8)	138 (94.5)	145 (94.8)
Completed Treatment*	128 (84.2)	107 (73.3)	121 (79.1)
Discontinued Treatment* n (%)	24 (15.8)	39 (26.7)	32 (20.9)
Discontinued Due to Adverse Events** n (%)	10 (41.7)	26 (66.7)	22 (68.8)
Protocol Violation	9 (37.5)	6 (15.4)	6 (18.8)
Other	5 (20.8)	7 (17.9)	4 (12.4)
Study 14CL308 (U.S.)			
Randomized (ITT)	220	222	224
Modified Intent to Treat (MITT)*	204 (92.7)	204 (91.9)	207 (92.4)
Completed Treatment*	187 (85.0)	184 (82.9)	176 (78.6)
Discontinued Treatment* n (%)	33 (15.0)	38 (17.1)	48 (21.4)
Discontinued Due to Adverse Events** n (%)	17 (51.5)	17 (44.7)	29 (60.4)
Protocol Violation	12 (36.4)	14 (36.8)	11 (22.9)
Other	4 (12.1)	7 (18.4)	8 (16.7)
Study 14CL313 (U.S., Canada)			
Randomized (ITT)	169	176	165
Modified Intent to Treat (MITT)*	155 (91.7)	165 (93.8)	149 (90.3)
Completed Treatment*	130 (76.9)	142 (80.7)	116 (70.3)
Discontinued Treatment* n (%)	39 (23.1)	34 (19.3)	49 (29.7)
Discontinued Due to Adverse Events** n (%)	19 (48.7)	15 (44.1)	28 (57.1)
Protocol Violation	14 (35.9)	10 (29.4)	16 (32.6)
Other	6 (15.4)	9 (26.5)	5 (10.2)
Study SB767905/001 (Europe, Australia, New Zealand)			
Randomized (ITT)	248	251	242
Modified Intent to Treat (MITT)*	237 (95.6)	239 (95.2)	229 (94.6)
Completed Treatment*	197 (79.4)	198 (78.9)	187 (77.3)
Discontinued Treatment* n (%)	50 (20.2)	51 (20.3)	55 (22.7)
Discontinued Due to Adverse Events** n (%)	12 (24.0)	12 (23.5)	9 (16.3)
Protocol Violation	15 (30.0)	13 (25.5)	21 (38.2)
Other	23 (46.0)	26 (51.0)	25 (45.5)

Source: Tables 8 and 9, pages 75 and 77, Study 14CL302 report / Tables 7 and 8, pages 70 and 72, Study 14CL308 report / Tables 7 and 8, pages 66 and 68, Study 14CL313 report / Tables 2 and 3, page 9 in Study SB767905/001 report.

* With respect to number of ITT subjects.

** With respect to number of all discontinuations.

The distribution of surgery types (bowel resection - BR, simple and radical total abdominal hysterectomy – sTAH and rTAH) is presented in Table 3.2. Bowel resection accounts for the majority of surgeries in each study.

Table 3.2
Number of Subjects for Each Surgery Type in MITT Population for Studies 14CL302, 14CL308, 14CL313, and SB767905/001

Study	Placebo			Alvimopan 6 mg			Alvimopan 12 mg		
	BR	rTAH	sTAH	BR	rTAH	sTAH	BR	rTAH	sTAH
14CL302 (N=424)	99	11	35	99	10	32	98	11	29
14CL308 (N=615)	142	36	29	137	36	31	139	35	30
14CL313 (N=469)	142	7	1	149	6	1	160	5	1
SB767905/001 (N=705)	229	-	-	237	-	-	239	-	-

Source: Statistical Reviewer's listing.

3.1.2 Study 14CL302 Results

The Sponsor's results for the primary efficacy endpoint and two important secondary endpoints for study 14CL302 in bowel resection and hysterectomy patients are presented in Table 3.3. The primary time-to-event efficacy endpoint of GI³ (recovery of GI function) in bowel resection and hysterectomy patients demonstrated a significant hazard ratio of 1.45 for 6 mg alvimopan compared to placebo (p=0.003) but not for 12 mg alvimopan compared to placebo (p=0.059).

Results for the two important secondary time-to-event endpoints in bowel resection and hysterectomy patients are as follow:

- "Ready for hospital discharge" demonstrated significant hazard ratios of 1.61 and 1.54 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.01)
- "Hospital discharge order written" demonstrated a significant hazard ratio of 1.50 for 6 mg alvimopan compared to placebo (p<0.001) but not for 12 mg alvimopan compared to placebo (p=0.171)

Table 3.3
Study 14CL302: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection and Hysterectomy Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
Placebo	145	19 (13.1)	93.6 (85.6, 98.4)		
Alvimopan 6 mg	141	10 (7.1)	78.2 (73.7, 88.3)	1.45 (1.13, 1.85)	0.003*
Alvimopan 12 mg	138	18 (13.0)	87.3 (76.7, 93.8)	1.28 (0.99, 1.64)	0.059
Ready for Hospital Discharge					
Placebo	103	8 (7.8)	101.0 (94.8, 112.8)		
Alvimopan 6 mg	103	2 (1.9)	93.1 (88.3, 96.1)	1.61 (1.21, 2.15)	<0.001*
Alvimopan 12 mg	101	8 (7.9)	94.1 (89.5, 98.3)	1.54 (1.14, 2.06)	0.004*
Hospital Discharge Order Written					
Placebo	145	5 (3.4)	114.8 (111.6, 117.3)		
Alvimopan 6 mg	141	2 (1.4)	107.9 (93.6, 112.6)	1.50 (1.18, 1.90)	<0.001*
Alvimopan 12 mg	138	6 (4.3)	112.8 (101.8, 115.4)	1.18 (0.93, 1.50)	0.171

Source: Tables 16 and 19, pages 85 and 89, Study 14CL302 Study Report.

^a Estimate (in hours) was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^b Hazard ratio of alvimopan to placebo was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^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.

My results for the primary efficacy endpoint and two important secondary endpoints for study 14CL302 in bowel resection patients are presented in Table 3.4. These results, except for the median time-to-event, are the same as the Sponsor's results for this group of patients. The primary time-to-event efficacy endpoint of GI³ in bowel resection patients demonstrated a significant hazard ratio of 1.48 for 6 mg alvimopan compared to placebo (p=0.009) but not for 12 mg alvimopan compared to placebo (p=0.086).

Results for the two important secondary time-to-event endpoints in bowel resection patients are as follow:

- "Ready for hospital discharge" demonstrated significant hazard ratios of 1.60 and 1.52 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values ≤ 0.01)
- "Hospital discharge order written" demonstrated a significant hazard ratio of 1.56 for 6 mg alvimopan compared to placebo (p=0.002) but not for 12 mg alvimopan compared to placebo (p=0.084)

The results for hysterectomy patients are presented in Table A.1 in Appendix 1. None of the results for the one primary and two important secondary efficacy endpoints demonstrate significance in this group of patients.

Table 3.4
Study 14CL302: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
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
Ready for Hospital Discharge					
Placebo	84	5 (6.0)	113.0 (99.3, 119.75)		
Alvimopan 6 mg	86	2 (2.3)	96.6 (94.0, 107.6)	1.60 (1.17, 2.19)	0.003*
Alvimopan 12 mg	84	5 (6.0)	99.5 (93.7, 112.8)	1.52 (1.11, 2.09)	0.010*
Hospital Discharge Order Written					
Placebo	99	5 (5.0)	136.4 (119.4, 140.9)		
Alvimopan 6 mg	99	2 (2.0)	116.4 (112.8, 117.5)	1.56 (1.17, 2.08)	0.002*
Alvimopan 12 mg	98	5 (5.1)	120.1 (115.6, 134.8)	1.29 (0.97, 1.72)	0.084

Source: Statistical Reviewer's 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.

3.1.3 Study 14CL308 Results

The Sponsor's results for the primary efficacy endpoint and two important secondary endpoints for study 14CL308 in bowel resection and hysterectomy patients are presented in Table 3.5. The primary time-to-event efficacy endpoint of GI³ (recovery of GI function) in bowel resection and hysterectomy patients did not demonstrate a significant hazard ratio for either 6 mg or 12 mg alvimopan compared to placebo.

Results for the two important secondary time-to-event endpoints in bowel resection and hysterectomy patients are:

- "Ready for hospital discharge" demonstrated significant hazard ratios of 1.26 and 1.28 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.025)
- "Hospital discharge order written" demonstrated significant hazard ratios of 1.31 and 1.28 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.025)

My results for the primary efficacy endpoint and two important secondary endpoints for study 14CL308 in bowel resection patients are presented in Table 3.6. These results, except for the median time-to-event, are the same as the Sponsor's results for this group of patients. The primary time-to-event efficacy endpoint of GI³ in bowel resection patients did not demonstrate a significant hazard ratio for either 6 mg or 12 mg alvimopan compared to placebo.

Table 3.5
Study 14CL308: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection and Hysterectomy Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
Placebo	207	20 (9.7)	94.8 (89.8, 98.7)		
Alvimopan 6 mg	204	18 (8.8)	90.7 (79.3, 95.2)	1.20 (0.98, 1.47)	0.080
Alvimopan 12 mg	204	19 (9.3)	86.4 (74.8, 93.3)	1.24 (1.01, 1.52)	0.038
Ready for Hospital Discharge					
Placebo	207	14 (6.8)	98.7 (95.1, 107.5)		
Alvimopan 6 mg	204	9 (4.4)	94.2 (88.7, 97.8)	1.26 (1.03, 1.54)	0.023*
Alvimopan 12 mg	204	14 (6.9)	93.2 (87.3, 96.6)	1.28 (1.04, 1.56)	0.017*
Hospital Discharge Order Written					
Placebo	207	7 (3.4)	116.4 (112.5, 120.5)		
Alvimopan 6 mg	204	5 (2.5)	109.3 (95.3, 114.3)	1.31 (1.07, 1.59)	0.008*
Alvimopan 12 mg	204	7 (3.4)	103.2 (94.5, 113.4)	1.28 (1.05, 1.56)	0.015*

Source: Tables 15 and 19, pages 81 and 85, Study 14CL308 Study Report.

^a Estimate (in hours) was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^b Hazard ratio of alvimopan to placebo was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^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.

Results for the two important secondary time-to-event endpoints in bowel resection patients are as follow:

- “Ready for hospital discharge” demonstrated significant hazard ratios of 1.33 and 1.40 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.025)
- “Hospital discharge order written” demonstrated significant hazard ratios of 1.42 and 1.56 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.01)

Table 3.6
Study 14CL308: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
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
Ready for Hospital Discharge					
Placebo	142	12 (8.4)	119.0 (111.1, 124.0)		
Alvimopan 6 mg	137	5 (3.6)	113.3 (103.1, 116.6)	1.33 (1.04, 1.70)	0.021*
Alvimopan 12 mg	139	11 (7.9)	107.5 (98.2, 115.0)	1.40 (1.09, 1.78)	0.008*
Hospital Discharge Order Written					
Placebo	142	7 (4.9)	139.8 (134.5, 150.1)		
Alvimopan 6 mg	137	4 (2.9)	120.5 (117.0, 132.1)	1.42 (1.12, 1.81)	0.004*
Alvimopan 12 mg	139	5 (3.6)	117.5 (115.0, 121.8)	1.56 (1.22, 1.98)	<0.001*

Source: Statistical Reviewer’s 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.

The results for hysterectomy patients are presented in Table A.2 in Appendix 1. None of the results for the one primary and two important secondary efficacy endpoints demonstrate significance in this group of patients.

3.1.4 Study 14CL313 Results

The Sponsor's results for the primary efficacy endpoint and two important secondary endpoints for study 14CL313 in bowel resection and hysterectomy patients are presented in Table 3.7. The primary time-to-event efficacy endpoint of GI³ (recovery of GI function) in bowel resection and hysterectomy patients demonstrated a significant hazard ratio of 1.28 and 1.54 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (p=0.047 and p<0.001).

Results for the two important secondary time-to-event endpoints in bowel resection and hysterectomy patients are as follow:

- "Ready for hospital discharge" demonstrated significant hazard ratios of 1.31 and 1.54 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.03)
- "Hospital discharge order written" demonstrated a significant hazard ratio of 1.42 for 12 mg alvimopan compared to placebo (p=0.003) but not for 6 mg alvimopan compared to placebo (p=0.070)

Table 3.7

Study 14CL313: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection and Hysterectomy Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
Placebo	149	26 (17.4)	103.0 (96.3, 115.1)		
Alvimopan 6 mg	155	16 (10.3)	95.8 (90.7, 100.4)	1.28 (1.004, 1.64)	0.047*
Alvimopan 12 mg	165	16 (9.7)	91.9 (81.8, 95.8)	1.54 (1.21, 1.96)	<0.001*
Ready for Hospital Discharge					
Placebo	149	21 (14.1)	111.6 (98.6, 117.7)		
Alvimopan 6 mg	155	14 (9.0)	97.6 (93.7, 105.1)	1.31 (1.03, 1.67)	0.028*
Alvimopan 12 mg	165	13 (7.9)	94.6 (91.6, 98.1)	1.54 (1.22, 1.96)	<0.001*
Hospital Discharge Order Written					
Placebo	149	18 (12.1)	125.7 (117.1, 138.1)		
Alvimopan 6 mg	155	10 (6.5)	117.1 (113.7, 123.4)	1.25 (0.98, 1.58)	0.070
Alvimopan 12 mg	165	9 (5.5)	115.2 (112.5, 117.8)	1.42 (1.12, 1.79)	0.003*

Source: Tables 15 and 18, pages 77 and 81, Study 14CL313 Study Report.

^a Estimate (in hours) was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^b Hazard ratio of alvimopan to placebo was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH).

^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.

My results for the primary efficacy endpoint and two important secondary endpoints for study 14CL313 in bowel resection patients are presented in Table 3.8. These results, except for the median time-to-event, are the same as the Sponsor's results for this group of patients. The primary time-to-event efficacy endpoint of GI³ in bowel resection patients demonstrated a significant hazard ratio of 1.49 for 12 mg alvimopan compared to placebo (p=0.002) but not for 6 mg alvimopan compared to placebo (p=0.084).

Results for the two important secondary time-to-event endpoints in bowel resection patients are as follow:

- "Ready for hospital discharge" demonstrated significant hazard ratios of 1.30 and 1.54 for 6 mg and 12 mg alvimopan, respectively, compared to placebo (both p-values < 0.04)
- "Hospital discharge order written" demonstrated a significant hazard ratio of 1.42 for 12 mg alvimopan compared to placebo (p=0.004) but not for 6 mg alvimopan compared to placebo (p=0.089)

Table 3.8
Study 14CL313: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
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*
Ready for Hospital Discharge					
Placebo	142	21 (14.8)	111.1 (97.6, 115.8)		
Alvimopan 6 mg	149	13 (8.7)	101.8 (94.6, 112.8)	1.30 (1.02, 1.67)	0.035*
Alvimopan 12 mg	160	13 (8.1)	95.0 (92.8, 100.2)	1.54 (1.21, 1.96)	<0.001*
Hospital Discharge Order Written					
Placebo	142	18 (12.7)	121.8 (115.8, 137.9)		
Alvimopan 6 mg	149	10 (6.7)	119.8 (115.2, 136.1)	1.24 (0.97, 1.58)	0.089
Alvimopan 12 mg	160	9 (5.6)	115.8 (112.7, 120.9)	1.42 (1.12, 1.81)	0.004*

Source: Statistical Reviewer's 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.

3.1.5 Study SB767905/001 Results

The Sponsor's results for the primary efficacy endpoint and two important secondary endpoints for study SB767905/001 in bowel resection patients are presented in Table 3.9. The primary time-to-event efficacy endpoint of GI³ (recovery of GI function) did not demonstrate a significant hazard ratio for either 6 mg or 12 mg alvimopan compared to placebo. Also, neither of the two important secondary time-to-event endpoints ("Ready for hospital discharge" and "Hospital discharge order written") demonstrated significant hazard ratios for either 6 mg or 12 mg alvimopan compared to placebo.

Table 3.9
Study SB767905/001: Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for the 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	N	Censored n (%)	Median (h) ^a (95% C.I.)	Hazard Ratio ^b (95% C.I.)	p-value ^c
Recovery of GI Function (GI³)					
Placebo	229	19 (8)	81.3 (65.8, 115.3)		
Alvimopan 6 mg	237	18 (8)	74.6 (58.8, 97.1)	1.22 (1.01, 1.47)	0.042
Alvimopan 12 mg	238	19 (8)	76.9 (62.4, 101.2)	1.13 (0.94, 1.37)	0.200
Ready for Hospital Discharge					
Placebo	229	29 (13)	137.5 (99.8, 173.4)		
Alvimopan 6 mg	237	30 (13)	125.3 (94.0, 165.0)	1.16 (0.96, 1.41)	0.134
Alvimopan 12 mg	238	28 (12)	127.2 (94.5, 166.9)	1.54 (0.92, 1.35)	0.287
Hospital Discharge Order Written					
Placebo	229	33 (14)	192.8 (161.3, 266.3)		
Alvimopan 6 mg	237	37 (16)	191.5 (158.6, 261.1)	1.08 (0.88, 1.31)	0.471
Alvimopan 12 mg	238	35 (15)	191.5 (158.6, 261.5)	1.07 (0.88, 1.30)	0.493

Source: Tables 4 and 5, pages 10 and 13, Study SB767905/001 Study Report.

^a Estimate (in hours) was calculated from a Cox proportional hazards model that included treatment only for bowel resection subjects only and confidence limits are the lower and upper quartiles.

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

^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.

I concur with the Sponsor's results for each efficacy endpoint except for the estimate of the median time-to-event. My results are presented below.

Table 3.10
Study SB767905/001: Median Time-to-event Results for the Primary Efficacy Endpoint of Recovery of GI Function and Two Secondary Efficacy Endpoints of Ready for Hospital Discharge and Hospital Discharge Order Written for 6 mg and 12 mg Doses of Alvimopan and for Placebo in Bowel Resection Patients

Time-to-event Endpoint	Median (h) ^a (95% C.I.)
Recovery of GI Function (GI³)	
Placebo	81.7 (75.7, 89.8)
Alvimopan 6 mg	73.8 (71.2, 77.7)
Alvimopan 12 mg	78.5 (73.8, 86.2)
Ready for Hospital Discharge	
Placebo	139.5 (126.4, 148.2)
Alvimopan 6 mg	120.4 (115.9, 135.2)
Alvimopan 12 mg	127.4 (118.3, 140.8)
Hospital Discharge Order Written	
Placebo	203.6 (190.5, 214.3)
Alvimopan 6 mg	191.8 (188.4, 196.0)
Alvimopan 12 mg	189.4 (186.2, 193.7)

Source: Statistical Reviewer's analysis.

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

3.1.6 Additional Analyses

The Clinical Reviewer requested that a responder analysis be performed in bowel resection patients. In addition to the response time used by the Sponsor, 108 hours (4.5 days), the Clinical Reviewer requested that the proportion of responders for each treatment group be calculated at the following times: 3 days, 4 days, 5 days, and 6 days. All patients are classified as responding or not, that is, achieving GI function, by each time. The difference in response rates between each alvimopan dose and placebo is calculated and significant differences are identified using a chi-square test and adjusting for multiple comparisons using Hochberg's procedure.

The results of this responder analysis are presented in Table B.1 in Appendix 2, which lists the proportion of responders and difference between active drug and placebo at each time for each study. There are four situations where the difference is significant:

- In Study 302, 6 mg alvimopan is different from placebo at the Day 4.5 (108 hrs) timepoint (p-value=0.0149).
- In Study 302, 12 mg alvimopan is different from placebo at the Day 4.5 (108 hrs) timepoint (p-value=0.0258).
- In Study 313, 12 mg alvimopan is different from placebo at the Day 5 (120 hr) timepoint (p-value=0.0071).
- In Study 313, 12 mg alvimopan is different from placebo at the Day 6 (144 hrs) timepoint (p-value=0.0056).

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

The Sponsor has presented analyses by gender, race, and age. There are no important differences among groups defined by values of these variables. Of greater interest are findings by surgery type, as described in section 4.2 below.

4.2 Other Special/Subgroup Populations

The subgroup populations of interest in this submission are bowel resection patients and hysterectomy patients, which are addressed in sections 3.1.2 through 3.1.5.

5. CONCLUSIONS

In bowel resection patients for the primary efficacy analysis, study 14CL302 is statistically significant for the 6 mg dose of alvimopan, study 14CL313 is statistically significant for the 12 mg dose of alvimopan, and studies 14CL308 and SB767905/001 are not statistically significant for either dose. These results do not show consistent evidence of efficacy for either the 6 mg or 12 mg dose of alvimopan for use in the recovery of GI function in bowel resection patients.

**Appears This Way
On Original**

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

APPENDIX 2

The following table presents the results of the responder analysis described in Section 3.1.6. The table lists the proportion of responders and difference between active drug and placebo at each time for each study.

Table B.1
Percent Responders at Different Timepoints for Each Treatment Group and Differences from Placebo in Percent Responders for Each Active Dose in Each Study

Recovery of GI Function (GI ^a)	N	Day 3 (72 hrs)		Day 4 (96 hrs)		Day 4.5 (108 hrs)		Day 5 (120 hrs)		Day 6 (144 hrs)	
		% Responder	Difference	% Responder	Difference	% Responder	Difference	% Responder	Difference	% Responder	Difference
Study 14CL302											
Placebo	99	15.2		39.4		47.5		61.6		76.8	
Alvimopan 6 mg	99	21.2	6.0	53.5	14.1	64.6	17.1*	75.8	14.2	85.9	9.1
Alvimopan 12 mg	98	16.3	1.1	44.9	5.5	63.3	15.8*	72.4	10.8	83.7	6.9
Study 14CL308											
Placebo	142	12.0		36.6		50.0		59.9		73.9	
Alvimopan 6 mg	137	11.0	-1.0	38.0	1.4	53.3	3.3	68.6	8.7	82.5	8.6
Alvimopan 12 mg	139	19.4	7.4	45.3	8.7	60.4	10.4	69.8	9.9	82.0	8.1
Study 14CL313											
Placebo	142	21.1		45.1		53.5		59.2		70.4	
Alvimopan 6 mg	149	22.2	1.1	46.3	1.2	59.1	5.6	64.4	5.2	78.5	8.1
Alvimopan 12 mg	160	24.4	3.3	50.0	4.9	64.4	10.9	73.8	14.6*	83.8	13.4*
Study SB767905/001											
Placebo	229	34.1		65.5		70.7		77.3		82.1	
Alvimopan 6 mg	237	42.6	8.5	68.8	3.3	74.3	3.6	79.8	2.5	86.9	4.8
Alvimopan 12 mg	238	38.5	4.4	63.6	-1.9	69.9	-0.8	77.0	-0.3	85.8	3.7

Source: Statistical reviewer's listing.

* p-value for difference is statistically significant based on chi-square test and after adjustment for multiple comparisons using Hochberg's procedure. In Study 302, the p-values for 6 mg and 12 mg at Day 4.5 (108 hrs) are 0.0149 and 0.0258, respectively. In Study 313, the p-values for 12 mg at Day 5 (120 hrs) and Day 6 (144 hrs) are 0.0071 and 0.0056, respectively.

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

/s/

Sonia Castillo
6/29/05 02:43:45 PM
BIOMETRICS

Stella Grosser
7/1/05 01:40:03 PM
BIOMETRICS