

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich
Application No. 11/083,167 Group No. 1617
Filed: March 17, 2005 Examiner: Kendra D. Carter
Confirmation No. 8002
For: Naltrexone Long Acting Formulations and Methods for Use

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

I, Elliot Ehrich, am the inventor of the subject matter of the above-identified application. I am also employed by Alkermes, Inc, the assignee of the above-identified application. My curriculum vitae is attached hereto as Exhibit D.

Background

The present invention is directed to the unexpected discovery that a single injection of a naltrexone-containing long-acting formulation provides systemic exposure to naltrexone (AUC) which is at least 2 fold higher over a 28 day period than the AUC of an oral regimen of 50 mg per day over a 28 day period. The invention which is described in the above identified application resulted from a discovery made during clinical trial testing of Alkermes' MEDISORB[®] (injectable) Naltrexone (tradename VIVITREX[®]). Due to the size of the lengthy full Clinical Study Report only relevant portions of the Clinical Study Report # ALK21-005 (the "Report") finalized November 9, 2004 is attached hereto as Exhibits A and B. I will be referring to this Report throughout my declaration.

Prior to obtaining the data discussed in the Report, it was believed that the doses of MEDISORB[®] Naltrexone suspension selected for the studies described in the Report (i.e. 190 mg and 380 mg) would result in total systemic exposure (AUC) which was similar to the AUC of an oral regimen of 50 mg per day naltrexone over a 28-day period. However,

as the data summarized in Table 8 of Exhibit A shows, the 380 mg dose has an AUC that is at least 3.3 times greater than the AUC of the per day dose of oral regimen of 50 mg per day naltrexone.

Data Analysis

Referring now to Table 8 of the Report shown in Exhibit A, note that the AUC_{0-t} ($AUC_{0-28days}$) for a single dose of MEDISORB[®] Naltrexone 380 mg on a per day basis can be calculated for Cohort A by dividing the AUC_{0-t} for Cohort A 120.6 by 28 days and for Cohort B, 137.8, by 28 days. For Cohort A, the per day 380 mg MEDISORB[®] Naltrexone AUC_{0-t} is 4.307 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.278. For Cohort B, the per day 380 mg MEDISORB[®] Naltrexone AUC_{0-t} is 4.921 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.468. This result was unexpected.

Based on the dose proportionality observed between 190 and 380 mg following a single dose, $AUC_{0-28days}$ for the 190 mg dose may reasonably be predicted to be approximately 2-fold higher than AUC following oral dosing of 50 mg per day for 28 days. This is also evident from Cohort A data showing about a 2-fold higher AUC for MEDISORB[®] Naltrexone 190 mg. This result was also unexpected.

Cited Reference US Pat No 6,306,425 ("Tice")

I have read the rejections from the Examiner and I have reviewed Tice cited by the Examiner. The Examiner claims that the data found in the table in column 14 of Tice indicates that the F-1' naltrexone-containing injectable formula described also exhibits an AUC which is 3.3 times higher over a period of 32 days as compared to the oral dosing of 50 mg per day of naltrexone for 32 days. This is incorrect.

Tice discloses an injectable formulation containing up to 350 mg of naltrexone. However, Tice does not disclose that the serum AUC of naltrexone is at least about 2 or 3.3 times greater than that achieved by the equivalent 50 mg/day oral administration over

the same period of time. Given that the oral naltrexone is delivered in a daily dose, it is necessary to either extrapolate (or actually measure) the AUC derived from the daily oral dose over the time period in which the AUC of the injectable extended dose is measured, or it is necessary to divide the AUC of the injectable extended dose over the number of days that AUC measurements of the injected extended dose are taken in order to arrive at the daily AUC of the extended dose and thereafter compare that measurement to the daily AUC of the daily oral dose. Therefore what is actually disclosed Tice is that the *extrapolated* 32 day AUC after a single dose of a 50 mg tablet of oral naltrexone (column 15, lines 62-65, 1600 mg naltrexone total dose) is similar to the AUC₀₋₃₂ day after injection of the F-1' naltrexone formulation tested in Tice.

The table in column 15 summarizes the data table in column 14 of Tice which compares the dose delivered in one day (with 50 mg) as compared to the delivery over 32 days. The mean dose is calculated by multiplying the mean daily dose over 32 days (to calculate the dose/day) is $27.8 \times 32 = 889.6$. The F-1' mean over 32 days achieved a 1051.6, which is less than twice the AUC. Looking at the data differently, the AUC over 32 days is 1051.6. The dose per day is 32.8 ($1051.6/32 = 32.8$), which is not twice 27.8, the per day dose for the 50 mg oral.

Comparison between Tice and the Present Application

Referring now to the graphs of Exhibit C, AUC data for Tice are taken from the text and table in column 14. According to the table, a single oral dose of 50 mg naltrexone was administered, and a mean AUC_{0-24h} value of 27.8 $\mu\text{g h/L}$ was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 300 mg injection of naltrexone resulted in a mean AUC_{0-32d} value of 1051.6 $\mu\text{g h/L}$. This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 32.9 $\mu\text{g h/L}$.

AUC data for MEDISORB® Naltrexone are taken from the text and table on page 6 of their clinical study report ALK21-005 (Exhibit B). According to the table on page 6 of

the Report, a single oral dose of 50 mg naltrexone was administered, and a mean $AUC_{0-\infty}$ value of 30.5 $\mu\text{g h/L}$ (1.270 ng days/mL) was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 190 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 1722 $\mu\text{g h/L}$ (71.75 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 53.8 $\mu\text{g h/L}$. A third set of data indicates that a single 380 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 3444 $\mu\text{g h/L}$ (143.5 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 107.6 $\mu\text{g h/L}$.

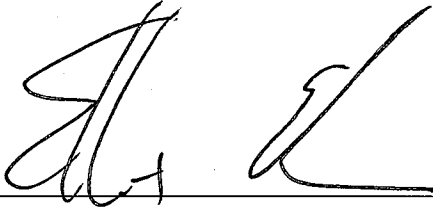
Comparisons between the graphed data from column 14 of Tice and the data from Exhibit B as shown in Exhibit C indicate that the 50 mg oral doses of Tice and Exhibit B and the single injectable dose of 300 mg of Tice result in similar average daily AUC values of 28-33 $\mu\text{g h/L}$. On the other hand, a single injectable dose of MEDISORB[®] Naltrexone 190 mg or MEDISORB[®] Naltrexone 380 mg (Alkermes) result in average daily AUC values that are, respectively, 1.6x (53.8 $\mu\text{g h/L}$) and 3.3x (107.6 $\mu\text{g h/L}$) greater than the average daily AUC value of 32.9 $\mu\text{g h/L}$, obtained from a single injectable dose of 300 mg in accordance with Tice.

Conclusion

Therefore, Tice does not disclose an injectable naltrexone formulation that has the presently claimed AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone. In addition, based on what was known in the prior art including Tice, it was unexpected that an injectable naltrexone formulation such as the MEDISORB[®] Naltrexone formulation would have an AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone.

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Declaration by Elliot Ehrich
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

A handwritten signature in black ink, consisting of stylized, cursive letters, positioned above a horizontal line.

Elliot Ehrich

Attachments: Exhibits A, B, C and D

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Table 8 Pharmacokinetic Parameters by Treatment for Naltrexone Following a Single Dose (Cohort A) and Repeat Doses (Cohort B) of Oral Naltrexone (50 mg) and Medisorb Naltrexone (190 and 380 mg) -- [Arithmetic Mean (SD)]

COHORT	PARAMETER	ORAL NALTREXONE 50 MG N = 28 (Cohort A) N = 14 (Cohort B)	MEDISORB NALTREXONE 190 MG N = 12	MEDISORB NALTREXONE 380 MG DOSE 1 of 4 N = 12	MEDISORB NALTREXONE 380 MG DOSE 4 of 4 N = 10
A (Single Dose)	C _{max} (ng/mL)	10.64 (6.92)	10.20 (6.67)	12.90 (4.67)	-
	t _{max} ^[a] (days)	0.04 (0.02-0.08)	2.00 (1.75-24.0)	2.00 (1.50-2.00)	-
	AUC _{0-τ} (ng*days/mL)	1.278 (0.589)	61.49 (14.78)	120.6 (19.6)	-
	AUC _{0-∞} (ng*days/mL)	1.270 (0.591) ^[b]	71.75 (9.06)	143.5 (29.3)	-
	t _{1/2} (days)	0.1611 (0.1065) ^[b]	7.363 (3.036)	4.948 (1.255)	-
	C _{max, ss} (ng/mL)	13.70 (10.63)	-	25.03 (12.69) ^[d]	27.96 (12.17)
B (Multiple Dose)	t _{max, ss} ^[a] (days)	0.035 (0.020-0.170)	-	2.00 (1.75-24.0) ^[e]	2.00 (1.75-3.00)
	AUC _{0-τ, ss} (ng*days/mL)	1.468 (0.940)	-	137.8 (24.4) ^[d]	159.9 (24.2)
	AUC _{0-∞, ss} (ng*days/mL)	1.559 (0.971) ^[e]	-	-	170.8 (29.6)
	t _{1/2, ss} (days)	0.1683 (0.0687) ^[e]	-	-	4.732 (1.333)
	C _{ave, ss} (ng/mL)	1.468 (0.940)	-	-	5.712 (0.866)
	C _{min, ss} (ng/mL)	0.05264 (0.10772)	-	-	1.338 (0.946)
	%Fluct (%)	918.0 (222.6)	-	-	466.3 (215.9)
	R	-	-	-	1.127 (0.155)

SD = Standard deviation; %Fluct = Percent fluctuation, calculated as (C_{max, ss}-C_{min, ss})/C_{ave, ss}*100; R = Accumulation ratio, calculated as AUC_{0-25day, Dose 4, ss}/AUC_{0-28day, Dose 1}
^[a] Presented as median (range); ^[b] N=27; ^[c] N=13; ^[d] C_{max}; ^[e] t_{max}; ^[f] AUC_{0-τ}
Source: Appendix 16.7, Table 8, Table 10, Table 12, Table 14, and Table 16.

CLINICAL STUDY REPORT

1.0 TITLE PAGE

Title: An Evaluation of the Steady-State and Single-Dose
Pharmacokinetics of Medisorb[®] Naltrexone in Healthy Subjects

Study Number: ALK21-005

Study Sponsor Alkermes, Inc.
88 Sidney Street
Cambridge, Massachusetts 02139 United States

Date of Report: Final: 09 November 2004

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EXHIBIT B

Statistical Methods: PK parameters were calculated from plasma concentration of naltrexone and 6 β -naltrexol using noncompartmental techniques. Descriptive statistics of PK parameters are summarized in Section 9.7.2.2.

Analysis of variance (ANOVA) models including treatment or analyte as fixed effects and subject as a random effect were fit to the data and the result was reported for the total population.

Data from subjects who received Medisorb Naltrexone 190 mg and 380 mg in Cohort A were used to assess dose proportionality (AUC and C_{max}) for naltrexone and 6 β -naltrexol. To assess the time invariance of naltrexone and 6 β -naltrexol PK following Medisorb Naltrexone administration, log-transformed AUC and $t_{1/2}$ were compared following single and multiple doses. Accumulation of naltrexone and 6 β -naltrexol following Medisorb Naltrexone administration was assessed by comparing $AUC_{0-\tau, Dose 4}$ with $AUC_{0-\tau, Dose 1}$ from subjects in Cohort B using a repeated measure ANOVA. Steady state was assessed by examination of the 90% confidence interval (CI) for the slope of the linear regression of log-transformed trough levels versus time. In addition, the theoretical time to steady state (by using the terminal elimination $t_{1/2}$ following a single dose) was also considered. The ratio of 6 β -naltrexol $AUC_{0-\infty}$ to naltrexone $AUC_{0-\infty}$ following oral naltrexone and Medisorb Naltrexone doses was analyzed using a repeated measure ANOVA model.

Descriptive statistics were provided for the appropriate safety parameters, including laboratory assessments and vital signs, by study group.

A secondary post-hoc analysis was performed to explore gender differences in the PK parameters AUC_{0-28} and C_{max} overall in all subjects administered a single Medisorb Naltrexone dose. An ANOVA model including gender was used to determine statistical differences in the overall PK parameters AUC_{0-28} and C_{max} between genders.

A complete description of statistical methods for this study is presented in Section 9.7.

RESULTS

Pharmacokinetics: PK parameters for naltrexone and 6 β -naltrexol following a single dose of oral naltrexone and Medisorb Naltrexone for subjects in Cohort A are presented in the table below:

ANALYTE	PARAMETER	ORAL 50 MG N=28	MEDISORB NALTREXONE 190 MG N=12	MEDISORB NALTREXONE 380 MG N=12
Naltrexone	$AUC_{0-\infty}$ (ng*days/mL)	1.270 (0.591) ^[a]	71.75 (9.06)	143.5 (29.3)
	C_{max} (ng/mL)	10.64 (6.92)	10.20 (6.67)	12.90 (4.67)
	t_{max} (days) ^[c]	0.04 (0.02-0.08)	2.00 (1.75-24.0)	2.00 (1.50-2.00)
6 β -naltrexol	$AUC_{0-\infty}$ (ng*days/mL)	35.71 (7.62)	175.4 (26.7) ^[b]	328.5 (80.2)
	C_{max} (ng/mL)	108.6 (35.6)	14.08 (7.84)	19.43 (6.35)
	t_{max} (days) ^[c]	0.04 (0.02-0.08)	3.00 (2.00-24.0)	3.00 (2.00-21.0)

Data are presented as arithmetic mean (SD).

^[a] N=27; ^[b] N=10

^[c] Presented as median (range).

PK parameters for naltrexone and 6 β -naltrexol following multiple doses of oral naltrexone and Medisorb Naltrexone for subjects in Cohort B are presented in the table below:

ANALYTE	PARAMETER	ORAL 50 MG N=14	MEDISORB NALTREXONE 380 MG Dose 1 of 4 N=12	MEDISORB NALTREXONE 380 MG Dose 4 of 4 N=10
Naltrexone	AUC _{0-∞, ss} (ng*days/mL)	1.559 (0.971) ^[a]	-	170.8 (29.6)
	C _{max, ss} (ng/mL)	13.70 (10.63)	25.03 (12.69) ^[c]	27.96 (12.17)
	t _{max, ss} (days) ^[b]	0.035 (0.020-0.170)	2.00 (1.75-24.0) ^[d]	2.00 (1.75-3.00)
6β-naltrexol	AUC _{0-∞, ss} (ng*days/mL)	47.20 (14.08)	-	318.3 (80.5)
	C _{max, ss} (ng/mL)	138.7 (36.0)	27.46 (11.78) ^[c]	34.23 (12.92)
	t _{max, ss} (days) ^[b]	0.04 (0.02-0.17)	3.00 (3.00-24.0) ^[d]	3.00 (2.00-3.00)

Data are presented as arithmetic mean (SD).

^[a] N=13

^[b] Presented as median (range).

^[c] C_{max}, ^[d] t_{max}

Dose-Proportionality: Ratios and 90% CIs for the assessment of dose-proportionality of naltrexone and 6β-naltrexol PK parameters following a single dose of Medisorb Naltrexone (Cohort A) are presented below.

ANALYTE	PARAMETER	GEOMETRIC LS MEANS		RATIO ^[a]	90% CI
		MEDISORB NALTREXONE 190 MG	MEDISORB NALTREXONE 380 MG		
Naltrexone	AUC _{0-∞} (ng*days/mL)	71.3	141	1.975	1.756, 2.222
	C _{max} (ng/mL)	8.34	12.1	1.455	0.991, 2.135
6β-naltrexol	AUC _{0-∞} (ng*days/mL)	174	320	1.843	1.590, 2.137
	C _{max} (ng/mL)	11.8	18.4	1.565	1.075, 2.279

^[a] Ratio of geometric LS means between the two doses.

Naltrexone and 6β-naltrexol AUC_{0-∞} and C_{max} were dose-proportional across the 190 and 380 mg dose range as the 90% CIs for all 4 parameters included the value of 2.

Time Invariance: Assessment of time invariance of naltrexone and 6β-naltrexol PK parameters following Medisorb Naltrexone 380 mg is presented below.

ANALYTE	PARAMETER	GEOMETRIC LS MEANS		RATIO ^[a]	90% CI
		COHORT A	COHORT B		
Naltrexone	AUC ^[b]	141	158	1.124	0.982, 1.287
	t _{1/2}	4.79	4.56	0.951	0.772, 1.172
6β-naltrexol	AUC ^[b]	320	287	0.896	0.754, 1.065
	t _{1/2}	5.52	5.02	0.908	0.755, 1.092

Cohort A: Single dose; Cohort B: Multiple dose

^[a] Ratio of geometric LS means between cohorts

^[b] Calculated as AUC_{0-∞} (Cohort A)/AUC_{0-τ, Dose 4} (Cohort B).

Naltrexone and 6β-naltrexol AUC and t_{1/2} did not change with time as the 90% CIs for all 4 parameters included the value of 1.

Accumulation: Assessment of accumulation of naltrexone and 6β-naltrexol following multiple doses of Medisorb Naltrexone 380 mg (Cohort B) is presented below.

ANALYTE	PARAMETER	GEOMETRIC LS MEANS		RATIO ^[a]	90% CI
		DOSE 1	DOSE 4		
Naltrexone	AUC _{0-∞} (ng*days/mL)	136	154	1.134	1.048, 1.226
6β-naltrexol	AUC _{0-∞} (ng*days/mL)	255	284	1.114	1.043, 1.191

^[a] Ratio of geometric LS means, calculated as AUC_{0-∞, Dose 4}/AUC_{0-∞, Dose 1} (Cohort B).

Naltrexone and 6β-naltrexol accumulation (13 and 11%, respectively) was not considered clinically relevant.

Steady State: Assessment of steady state of naltrexone and 6β-naltrexol following multiple doses of Medisorb Naltrexone 380 mg (Cohort B) is presented below.

ANALYTE	SLOPE ^[a]	90% CI
Naltrexone	-0.001	-0.004, 0.002
6β-naltrexol	-0.000	-0.004, 0.003

^[a] Slope was determined based on the LS mean of log trough levels following doses 1 – 4 in Cohort B

Based on results of the linear regression analysis, both naltrexone and 6β-naltrexol concentrations reached steady state at the end of the dosing interval following the first dose.

Metabolite:parent AUC Ratio: Assessment of metabolite:parent AUC ratios following oral naltrexone 50 mg and Medisorb Naltrexone 190 mg and 380 mg, are presented below.

COHORT	DOSE GROUP	AUC GEOMETRIC LS MEANS (ng*days/mL)		Ratio ^[a]	90% CI
		NALTREXONE	6β-NALTREXOL		
A	Oral (50 mg)	1.16	35.0	30.253	25.969, 35.244
	Medisorb Naltrexone 190 mg	71.3	173	2.432	2.253, 2.626
	Medisorb Naltrexone 380 mg	141	320	2.274	2.117, 2.442
B	Oral (50 mg)	1.24	34.7	28.074	20.752, 37.979
	Medisorb Naltrexone 380 mg	158	287	1.813	1.598, 2.056

^[a] AUC_{0-∞} and AUC_{0-τ} were used to calculate the ratio and 90% CI following single and multiple doses, respectively.

The metabolite:parent AUC ratio following oral naltrexone administration was approximately 30, whereas, the ratio following Medisorb Naltrexone administration was approximately 2.

Gender Differences: Assessment of gender differences of naltrexone and 6β-naltrexol following a single dose of Medisorb Naltrexone is presented below.

ANALYTE	PARAMETER	RATIO ^[a]	90% CI ^[b]
Naltrexone	C _{max} (ng/mL)	0.677	0.469, 0.979
	AUC ₀₋₂₈ (ng*days/mL)	1.039	0.823, 1.313
6β-naltrexol	C _{max} (ng/mL)	0.742	0.536, 1.027
	AUC ₀₋₂₈ (ng*days/mL)	1.042	0.822, 1.321

^[a] The ratio was obtained by exponentiating the difference in the LS means of the natural log-transformed parameters. Presented as Female/Male

^[b] 90% CIs for the ratio of Females to Males.

Naltrexone and 6β-naltrexol C_{max} were lower in females compared with males. Naltrexone and 6β-naltrexol AUC₀₋₂₈ were similar between females and males following a single dose of Medisorb Naltrexone.

**Safety and
Tolerability:**

No serious adverse events (SAEs) occurred. All AEs were mild in severity, with the exception of 1 event of moderate intensity; no subject experienced a severe AE during the study in any study group.

Oral Naltrexone

Four of the 28 subjects enrolled in Cohort A and 6 of the 14 subjects enrolled in Cohort B reported at least one AE following oral administration. All AEs reported during the oral period were mild in severity and classified as possibly related to study drug by the Investigator. The most common AE in Cohort A was dizziness. In Cohort B, nausea and somnolence were the most common AEs.

Medisorb Naltrexone – Cohort A

Two of 12 subjects administered Medisorb Naltrexone 190 mg and 1 of 12 subjects administered Medisorb Naltrexone 380 mg reported at least one AE. All AEs reported for Cohort A were mild in severity and classified as possibly related to study drug by the Investigator. No AEs were reported by subjects administered placebo.

Medisorb Naltrexone – Cohort B

Four of 12 subjects administered Medisorb Naltrexone 380 mg reported at least one AE. All AEs reported for Cohort B were mild in severity with the exception of 1 subject who reported diarrhea of moderate severity. The most common AEs in Cohort B were vomiting and dizziness. No AEs were reported by subjects administered placebo.

Three subjects reported injection site reactions (ISRs) following IM administration of Medisorb Naltrexone 380 mg. All ISRs were reported following single dose administration in Cohort A or following Dose 1 in Cohort B. Subject 205-021 reported induration and tenderness; Subject 205-102 reported induration, 1-inch ecchymotic area, tenderness, and redness; and Subject 205-103 reported induration and tenderness. All reported ISRs resolved without sequelae.

There were no trends or clinically meaningful changes from baseline observed in mean or median clinical laboratory values or vital signs for any of the study groups.

There were no trends or clinically meaningful changes observed in ECG values for subjects in this study. QTcB and QTcF interval data were comparable for all dose groups. There was no evidence of an effect on cardiac conduction as detailed by the 12-lead ECG intervals duration.

Efficacy:

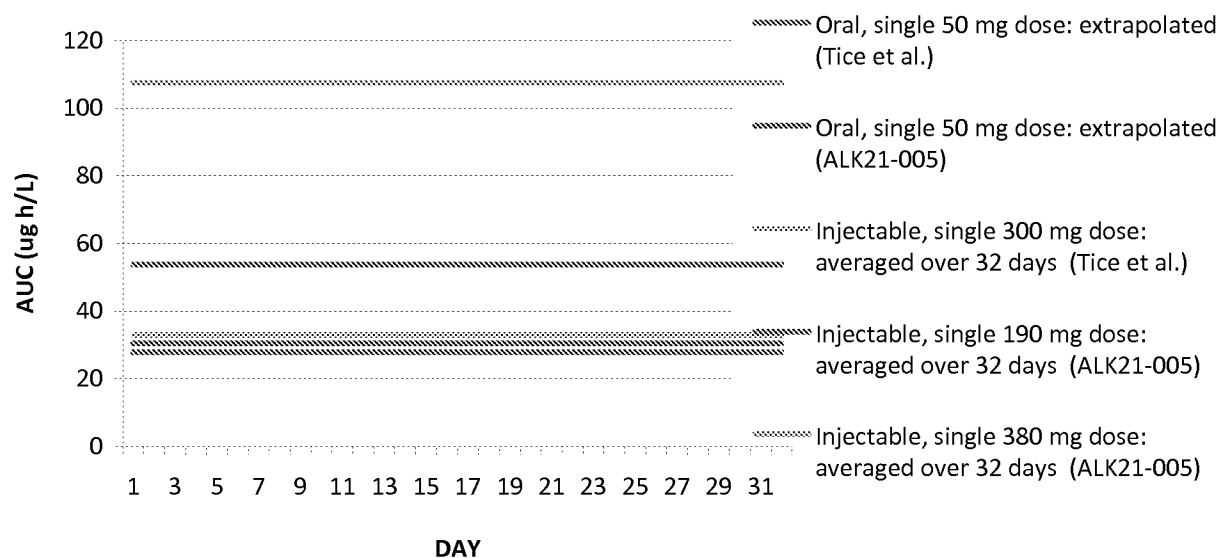
No efficacy parameters were evaluated during this clinical trial.

Conclusions:	▪ Naltrexone and 6β-naltrexol AUC_{0-∞} and C_{max} were dose-proportional following single administration of Medisorb Naltrexone across the 190 to 380 mg dose range. ▪ Based on time invariance analysis of AUC and t_{1/2}, the PK of naltrexone and 6β-naltrexol was similar between single and multiple doses of Medisorb Naltrexone 380 mg. ▪ Accumulation of naltrexone and 6β-naltrexol was 13 and 11%, respectively, following multiple doses of Medisorb Naltrexone. ▪ Steady state was reached for naltrexone and 6β-naltrexol at the end of the dosing interval following the first dose of Medisorb Naltrexone 380 mg. ▪ The metabolite:parent AUC ratios following Medisorb Naltrexone and oral administration were approximately 2 and 30, respectively. Overall, naltrexone exposure following Medisorb Naltrexone was higher and 6β-naltrexol exposure was lower following Medisorb Naltrexone 380 mg administration compared with the oral naltrexone 50 mg administration. ▪ Naltrexone C_{max} was approximately 1/3 lower in females compared with males, however, overall exposure (AUC) was similar between males and females. ▪ Single and multiple doses of Medisorb Naltrexone were well tolerated based on the number and severity of reported AEs. There were no trends or clinically meaningful changes from baseline observed in mean or median clinical laboratory values or vital sign findings for any of the study groups. ▪ There were no trends or clinically meaningful changes observed in ECG values for subjects in this study. There was no evidence of an effect on cardiac conduction as detailed by the 12-lead ECG intervals duration
GCP Compliance:	Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The Alkermes commitment is compliance with this standard to provide assurance that the rights, safety, and well-being of trial subjects will be protected, consistent with the principles that have their origin in the Declaration of Helsinki.
Date of the Report:	Final: 09 November 2004

AUC ug h/L					
Oral			Injectable		
50mg		50mg	300mg	190mg	380mg
DAY	Tice et al	ALK21-005	Tice et al	ALK21-005	ALK21-005
1	27.8	30.5	32.9	53.8	107.6
2	27.8	30.5	32.9	53.8	107.6
3	27.8	30.5	32.9	53.8	107.6
4	27.8	30.5	32.9	53.8	107.6
5	27.8	30.5	32.9	53.8	107.6
6	27.8	30.5	32.9	53.8	107.6
7	27.8	30.5	32.9	53.8	107.6
8	27.8	30.5	32.9	53.8	107.6
9	27.8	30.5	32.9	53.8	107.6
10	27.8	30.5	32.9	53.8	107.6
11	27.8	30.5	32.9	53.8	107.6
12	27.8	30.5	32.9	53.8	107.6
13	27.8	30.5	32.9	53.8	107.6
14	27.8	30.5	32.9	53.8	107.6
15	27.8	30.5	32.9	53.8	107.6
16	27.8	30.5	32.9	53.8	107.6
17	27.8	30.5	32.9	53.8	107.6
18	27.8	30.5	32.9	53.8	107.6
19	27.8	30.5	32.9	53.8	107.6
20	27.8	30.5	32.9	53.8	107.6
21	27.8	30.5	32.9	53.8	107.6
22	27.8	30.5	32.9	53.8	107.6
23	27.8	30.5	32.9	53.8	107.6
24	27.8	30.5	32.9	53.8	107.6
25	27.8	30.5	32.9	53.8	107.6
26	27.8	30.5	32.9	53.8	107.6
27	27.8	30.5	32.9	53.8	107.6
28	27.8	30.5	32.9	53.8	107.6
29	27.8	30.5	32.9	53.8	107.6
30	27.8	30.5	32.9	53.8	107.6
31	27.8	30.5	32.9	53.8	107.6
32	27.8	30.5	32.9	53.8	107.6

EXHIBIT C

Naltrexone Average Daily AUC Levels



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- Executive Officer 2006-Present
- Vice President, Science and Development, Chief Medical Officer 2003-2007
- Vice President, Medical Affairs 2000-2003

PRIOR EMPLOYMENT

Merck & Co., Inc. 1993-2000

- Senior Director, Clinical Research, Pulmonary-Immunology 1998 - 2000
- Director, Clinical Research, Pulmonary-Immunology 1995 - 1998
- Associate Director, Clinical Pharmacology 1993 -1995

EDUCATION

<u>SCHOOL</u>	<u>DATE</u>	<u>MAJOR</u>	<u>DEGREE</u>
Princeton University Princeton, NJ	1977 - 1981	Biochemistry	B.A., <i>Magna cum Laude</i> , <i>Phi Beta Kappa</i>
Columbia University College of Physicians and Surgeons, New York, NY	1982 - 1986	Medicine	M.D.

EXHIBIT D

POSTGRADUATE TRAINING

Stanford University, Stanford, CA 1986 - 1993

Internship and Residency, Department of Medicine
Clinical Fellowship, Rheumatology, Division of Immunology and Rheumatology
Cancer Research Institute/FW. Kirby Foundation Postdoctoral Fellowship 1990-1993,
Laboratory of Dr. Mark Davis, HHMI, Department of Microbiology and Immunology

European Molecular Biology Laboratory (EMBL) 1981, 1985
Heidelberg, Germany, Research Associate, Laboratory Dr. Hans Lehrach

ACADEMIC APPOINTMENT

Clinical Assistant Professor of Medicine 1997-Present
Robert Wood Johnson Medical School

PROFESSIONAL HONORS

Fellow, American College of Rheumatology 1993 - Present
American College of Rheumatology Senior Rheumatology Scholar Award
Board Certification, Rheumatology, American Board of Internal Medicine 1993-2003
Board Certification, Internal Medicine, American Board of Internal Medicine 1989-Present
Board Certification, National Board of Medical Examiners 1986-Present

PUBLICATIONS

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