Appendix Table 10.1.1.f Demographic and Baseline Characteristics – ALK21-003

	Treatment Group			
	All Subjects	Placebo	190mg	380mg
No. of Subjects in the ITT Population	624	209	210	205
Sex (N,%)[1]				
Male	423 (67.8)	143 (68.4)	142 (67.6)	138 (67.3)
Female	201 (32.2)	66 (31.6)	68 (32.4)	67 (32.7)
Age (years)				
N	624	209	210	205
Mean	44.7	44.7	44.6	45.0
Std.Dev.	10.6	10.8	10.8	10.1
Median	44.5	44.0	44.0	45.0
Min-Max	19- 79	21- 79	19- 72	21- 72
Race / Ethnicity (N,%)[1]				
Caucasian	521 (83.5)	180 (86.1)	169 (80.5)	172 (83.9)
African American	50 (8.0)	17 (8.1)	17 (8.1)	16 (7.8)
Hispanic	32 (5.1)	7 (3.3)	15 (7.1)	10 (4.9)
Other	15 (2.4)	3 (1.4)	7 (3.3)	5 (2.4)
Asian	3 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Native American	3 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Male's Weight (kg)				
N	423	143	142	138
Mean	88.5	86.4	88.6	90.7
Std.Dev.	18.1	15.6	19.1	19.3
Median	85.0	82.0	85.0	89.0
Min-Max	50-159	59-137	51-159	50-156
Female's Weight (kg)				
N	200	66	68	66
Mean	71.3	72.2	70.8	71.0
Std.Dev.	16.2	16.4	15.3	17.3
Median	67.0	68.0	66.9	66.0
Min-Max	46-139	46-113	50-120	46-139
Male's Height (cm)				
N	422	143	141	138
Mean	178.3	178.1	178.1	178.8
Std.Dev.	7.2	7.3	7.5	6.9
Median	178.0	178.0	178.0	179.5
Min-Max	155-205	157-195	155-205	165-198

(table continues on next page)

(Source: Applicant's Table 6, Module 5, Clinical Study Report, ALK21-003, P. 50)

Appendix Table 10.1.1.g Demographic and Baseline Characteristics (contd.)

	Treatment Group			
	All Subjects	Placebo	190mg	380mg
Female's Height (cm)				
N	200	66	68	66
Mean	165.1	165.3	165.8	164.3
Std.Dev.	6.5	6.1	6.6	6.9
Median	165.0	165.0	166.0	165.0
Min-Max	150-185	155-185	150-180	150-183
Site (N,%)[1]				
217	46 (7.4)	15 (7.2)	15 (7.1)	16 (7.8)
225	40 (6.4)	14 (6.7)	12 (5.7)	14 (6.8)
209	39 (6.3)	14 (6.7)	12 (5.7)	13 (6.3)
210	38 (6.1)	14 (6.7)	12 (5.7)	12 (5.9)
215	36 (5.8)	12 (5.7)	12 (5.7)	12 (5.9)
214	35 (5.6)	11 (5.3)	12 (5.7)	12 (5.9)
213	33 (5.3)	11 (5.3)	11 (5.2)	11 (5.4)
208	32 (5.1)	10 (4.8)	13 (6.2)	9 (4.4)
224	31 (5.0)	10 (4.8)	10 (4.8)	11 (5.4)
218	31 (5.0)	11 (5.3)	10 (4.8)	10 (4.9)
216	30 (4.8)	11 (5.3)	10 (4.8)	9 (4.4)
212	30 (4.8)	10 (4.8)	10 (4.8)	10 (4.9)
202	27 (4.3)	10 (4.8)	9 (4.3)	8 (3.9)
230	27 (4.3)	8 (3.8)	10 (4.8)	9 (4.4)
221	26 (4.2)	8 (3.8)	9 (4.3)	9 (4.4)
211	25 (4.0)	8 (3.8)	9 (4.3)	8 (3.9)
227	20 (3.2)	7 (3.3)	7 (3.3)	6 (2.9)
229	17 (2.7)	5 (2.4)	6 (2.9)	6 (2.9)
228	17 (2.7)	5 (2.4)	6 (2.9)	6 (2.9)
220	13 (2.1)	4 (1.9)	4 (1.9)	5 (2.4)
207	12 (1.9)	4 (1.9)	4 (1.9)	4 (2.0)
226	8 (1.3)	3 (1.4)	3 (1.4)	2 (1.0)
219	6 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
223	5 (0.8)	2 (1.0)	2 (1.0)	1 (0.5)
Treatment Centers (N,%)[1]				
Addiction	303 (48.6)	104 (49.8)	102 (48.6)	97 (47.3)
Both Addiction/Research	109 (17.5)	36 (17.2)	36 (17.1)	37 (18.0)
Research	212 (34.0)	69 (33.0)	72 (34.3)	71 (34.6)
Subjects' Treatment Goal[1]				
Total Abstinence	270 (43.3)	90 (43.1)	90 (42.9)	90 (43.9)
Total Abstinence, but a lapse is possible	64 (10.3)	19 (9.1)	24 (11.4)	21 (10.2)
Occasional Use	191 (30.6)	68 (32.5)	61 (29.0)	62 (30.2)
Temporary Abstinence	9 (1.4)	4 (1.9)	3 (1.4)	2 (1.0)
Regular use but quantity controlled	75 (12.0)	23 (11.0)	29 (13.8)	23 (11.2)
No goal	15 (2.4)	5 (2.4)	3 (1.4)	7 (3.4)
No. of Subjects with Lead-in Drinking (N,%)[1]	571 (91.5)	190 (90.9)	193 (91.9)	188 (91.7)
% Heavy Drinking Days 30 Days Pre First Dose				
N	624	209	210	205
Mean	64.9	65.2	65.6	64.0
Std.Dev.	25.7	24.8	26.4	25.9
Median	63.3	66.7	63.3	63.3
Min-Max	0-100	0-100	0-100	0-100

(table continues on next page)

(Source: Applicant's Table 6, Module 5, Clinical Study Report, ALK21-003, P. 51)

Appendix Table 10.1.1.h Demographic and Baseline Characteristics (contd.)

	Treatment Group			
	All Subjects	Placebo	190mg	380mg
No. of Heavy Drinking Days 30 Days Pre First Dose				
N	624	209	210	205
Mean	19.5	19.5	19.7	19.2
Std.Dev.	7.7	7.5	7.9	7.8
Median	19.0	20.0	19.0	19.0
Min-Max	0- 30	0- 30	0- 30	0- 30
% Drinking Days 30 Days Pre First Dose				
N	624	209	210	205
Mean	76.4	76.4	76.7	76.1
Std.Dev.	23.1	22.9	23.2	23.3
Median	83.3	80.8	83.3	83.3
Min-Max	0-100	0-100	0-100	0-100
No. of Drinking Days 30 Days Pre First Dose				
N	624	209	210	205
Mean	22.9	22.9	23.0	22.8
Std.Dev.	6.9	6.9	7.0	7.0
Median	25.0	24.0	25.0	25.0
Min-Max	0- 30	0- 30	0- 30	0- 30
Alcohol Dependence Scale Score*				
N	306	100	103	103
Mean	17.1	16.6	17.8	16.9
Std.Dev.	7.4	7.2	7.2	7.9
Median	16.5	16.0	17.0	16.0
Min-Max	1- 42	2- 42	4- 40	1- 39
Unemployed at Baseline[1]				
No	533 (85.4)	177 (84.7)	178 (84.8)	178 (86.8)
Yes	89 (14.3)	31 (14.8)	31 (14.8)	27 (13.2)
Attended Any Self Help Groups at Baseline?[1]				
No	553 (88.6)	185 (88.5)	187 (89.0)	181 (88.3)
Yes	69 (11.1)	23 (11.0)	22 (10.5)	24 (11.7)
Smoking Status at Baseline?[1]				
No	328 (52.6%)	120 (57.4%)	103 (49.0%)	105 (51.2%)
Yes	293 (47.0%)	88 (42.1%)	106 (50.5%)	99 (48.3%)
Unknown	3 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)

[1]Percentages are out of the number of subjects in the ITT Population
*The ADS was added to the protocol in April 2002, after enrollment had begun. Subjects enrolled prior to that date did not complete the questionnaire.

(Source: Applicant's Table 6, Module 5, Clinical Study Report, ALK21-003, P. 52)

Applicant's Efficacy Analysis

Overview:

The Applicant found that, with respect to the primary endpoint, treatment with Medisorb Naltrexone 380-mg was associated with a 25% decrease in the event rate of heavy drinking compared to treatment with placebo, and the difference was statistically significant. The event rate of heavy drinking in the 190-mg group was also less than placebo (17% less). However, this

difference did not reach statistical significance. Similar results were obtained with the definition of heavy drinking was made slightly more stringent (≥ 3/4 drinks per day instead of ≥ 4/5 drinks per day).

Among patients abstinent at baseline, the event rate of heavy drinking was even more reduced in the Medisorb Naltrexone 190- and 380-mg groups. Again, however, the difference was statistically significant only for the 380-mg group.

The effects of treatment on an individual patient basis were explored using a responder analysis. Treatment response was defined using various cut-offs of the average number of heavy drinking days per month. Alkermes found that there were more responders in the 380-mg group than in the 190-mg or placebo groups, especially at the broader (i.e. less stringent) cut-offs for treatment response.

Due to the DSI findings of protocol violations that could potentially have led to reporting or assessment biases, the Applicant was asked to reanalyze the efficacy data after excluding subjects from these two sites. Alkermes found that the reduction in the event rate of heavy drinking in the Medisorb Naltrexone groups was lower than that observed upon analysis of the entire database (reduction in heavy drinking compared to placebo was 6% for the 190-mg group and 12% for the 380-mg group). Alkermes considered these results to still show a positive overall treatment effect.

In summary, based on its analyses, Alkermes concluded that treatment with Medisorb Naltrexone 380-mg (but not 190-mg) is efficacious in the treatment of alcohol dependence.

Primary Efficacy Analysis: Event rate of heavy drinking

a) Medisorb Naltrexone vs. pooled placebo group

The primary efficacy analysis was performed on all heavy drinking events from the first day of treatment up to 30 days following the last dose of study drug. A heavy drinking event was defined as a day on which alcohol consumption was ≥ 5 drinks (men) and ≥ 4 drinks (women). The analysis used 8 strata corresponding to predefined factors used in the dynamic randomization: gender (male/female), lead-in-drinking (yes/no), treatment goal of abstinence (yes/no).

Appendix Table 10.1.1.i (next page) displays hazard ratios for the event rate of event drinking for the Medisorb Naltrexone 190-mg and 380-mg groups, compared to the pooled placebo group. The table shows that, compared to placebo, treatment with Medisorb Naltrexone 380-mg was associated with a 25% decrease in the event rate of heavy drinking and this difference was statistically significant ($p = 0.0245$). Treatment with Medisorb Naltrexone 190-mg resulted in a 17% decrease in the event rate of heavy drinking, but this difference was not statistically significant ($p = 0.744$).

Appendix Table 10.1.1.i: Applicant's Analysis: Event rate of heavy drinking (≥ 4 drinks/day (women) or ≥ 5 drinks/day (men)) vs. pooled placebo groups – Study ALK21-003

Analysis*	Medisorb Naltrexone 190-mg vs. Placebo			Medisorb Naltrexone 380-mg vs. Placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Stratified by 8 strata	-0.186	0.83 (0.68, 1.0)	0.0744	-2.87	0.75 (0.60, 0.94)	0.0123

* Not adjusted for baseline percent heavy drinking
(Source: Applicant's ALK21-003 Study Report, Appendix Tables, Table 14.2.1, P. 39)

b) Medisorb Naltrexone 190-mg vs. 2-mL placebo, and 380-mg vs. 4-mL placebo

Treatment comparisons were repeated using the respective placebo to the Medisorb Naltrexone dose and the 8 randomization strata (Appendix Table 10.1.1.j). Comparisons using 7 strata and an unstratified analysis were also conducted. A 7-strata analysis was used because one of the strata (gender: female, lead-in-drinking: no, treatment goal of abstinence: yes) consisted of only 5 subjects, none of whom was assigned to the placebo group. Since there were no placebo patients in this stratum, the preplanned analysis would exclude data from this stratum. Therefore, the 2 smallest strata were collapsed to permit a stratified analysis that included all subjects.

Using the 8 strata analysis, the treatment effects for both the 190-mg vs. 2-mL and the 380-mg vs. 4-mL comparison were statistically significant. Compared to treatment with the respective placebo groups, treatment Medisorb Naltrexone reduced the event rate of heavy drinking by 76% and 35%, respectively (p = < 0.001 each) However, the treatment effect was not significant based on the 7 strata or on the unstratified analysis:

Appendix Table 10.1.1.j: Applicant's Analysis: Event rate of heavy drinking, individual placebo groups – ALK21-003

Analysis*	Vivitrex 190-mg vs. 2-mL placebo			Vivitrex 380-mg vs. 4-mL placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Stratified by 8 strata	-1.406	0.245 (0.192,0.214)	<0.0001	-0.420	0.650 (0.502,0.842)	0.0011
Stratified by 7 strata	-0.150	0.861 (0.671,1.104)	0.2276	-0.456	0.624 (0.489,0.822)	0.0006
Unstratified	-0.029	0.971 (0.725,1.282)	0.8259	-0.254	0.702 (0.526, 0.919)	0.0100

* Not adjusted for baseline percent heavy drinking
(Source: Applicant's Tables 14.2.6.2, 14.6.2.4, and 14.2.6.8, Demographic Data Summary Figures and Tables, Clinical Study Report ALK21-003, P. 62, 64, and 68)

The effect of placebo volume on the event rate of heavy drinking was also evaluated. The difference between the 2-mL and the 4-mL placebo group was not statistically significant regardless of which stratification method was utilized.

Appendix Table 10.1.1.k Applicant's Analysis: Event rate of heavy drinking - Effect of placebo volume – ALK21-003

Analysis	Hazard ratio (p- value) 4-mL placebo vs. 2-mL placebo
Stratified by 8 strata	1.102 (0.4794)
Stratified by 7 strata	1.102 (0.4794)
Unstratified	1.169 (0.3040)

REVIEWER COMMENT:
The stratified and unstratified analyses comparing each Medisorb Naltrexone dose with its respective placebo group show different outcomes than that of the 8-stratum analysis of the Medisorb Naltrexone doses and the pooled placebo group. This suggests that the placebo groups are distinct. However, per the Applicant's evaluation, there does not appear to be an effect of placebo volume on the efficacy outcome. Therefore, pooling of the placebo groups for comparison of efficacy is acceptable

c) Imputing Heavy Drinking Days for Missing Data
Alkermes constructed a sensitivity analysis for the event rate of heavy drinking, in which missing data during the middle of the study (i.e., between randomization and discontinuation) were imputed as heavy drinking days. A total of 136 applicable drinking days were imputed to a heavy drinking day; 21 in the placebo group, 64 in the Medisorb Naltrexone 190 mg group, and 51 in the Medisorb Naltrexone 380 mg group. The results of this analysis showed statistically significant reductions with Medisorb Naltrexone 380 mg versus placebo for the 8-strata, 7-strata, and unstratified analysis. These results were similar to those of the primary efficacy analysis in which no imputation strategy was implemented for missing data.

Appendix Table 10.1.1.l: Applicant's Analysis: Event rate of heavy drinking, Imputing heavy drinking days for missing data – ALK21-003

Analysis*	Vivitrex 190-mg vs. 2-mL placebo			Vivitrex 380-mg vs. 4-mL placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Stratified by 8 strata	-0.180	0.825 (0.681,1.022)	0.0815	-0.256	0.700 (0.562,0.872)	0.0016
Stratified by 7 strata	-0.179	0.826 (0.682,1.022)	0.0826	-0.275	0.687 (0.550,0.858)	0.0009
Unstratified	-0.106	0.900 (0.726,1.116)	0.2256	-0.279	0.756 (0.596,0.959)	0.0210

* Not adjusted for baseline percent heavy drinking
(Source: Applicant's Tables 14.2.7.1, 14.2.7.3, and 14.2.7.5, Demographic Data Summary Figures and Tables, Clinical Study Report ALK21-003, P. 70, 72, and 74)

REVIEWER COMMENT:
Data missing due to premature withdrawal from the study (i.e. prior to Day 169) were not imputed as heavy drinking days. As already shown, 222 patients discontinued treatment prematurely, and these patients' missing days of data were not accounted for in the Applicant's sensitivity analysis. Therefore, this was neither an adequate nor an appropriate strategy to evaluate the effect of missing data on the efficacy results.

Supplemental analyses of the primary efficacy endpoint, event rate of heavy drinking

a) Sensitivity analysis of the definition of heavy drinking

The rate of heavy drinking was reanalyzed using a modified definition of heavy drinking (≥4 drinks/day for males and ≥3 drinks/day for females). The event rate of heavy drinking was calculated using the pooled placebo group for comparison. Results for this analysis were similar to those of the primary analysis.

Appendix Table 10.1.1.m: Applicant's Analysis: Event rate of heavy drinking - Alternate definition of heavy drinking (≥ 4/3 drinks per day)

Analysis*	Vivitrex 190-mg vs. 2-mL placebo			Vivitrex 380-mg vs. 4-mL placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Unstratified	-0.075	0.928 (0.768,1.120)	0.4222	-0.222	0.801 (0.656,0.978)	0.0292

(Source: Applicant's Table 14.2.8.1, Demographic Data Summary Figures and Tables, Clinical Study Report ALK21-003, P. 75)

b) Controlling for baseline percent heavy drinking

Baseline percent heavy drinking was a highly influential predictor variable for heavy drinking overall in the study. For each increase of 10% in baseline percent heavy drinking (i.e. ≥ 5/4 drinks per day), there was an increase of 26% in the event rate of heavy drinking during the study period (P<0.0001).

Controlling for baseline heavy drinking, where baseline was defined as 30 days prior to the first drug dose, the analysis showed that patients in the Medisorb Naltrexone 380 mg group experienced a 25% reduction (hazard ratio 0.748) in the event rate of heavy drinking compared with subjects in the placebo group (p = 0.0047). Patients in the Medisorb Naltrexone 190 mg group showed a 14% (hazard ratio 0.861) reduction in the event rate of heavy drinking compared with subjects in the placebo group that was not statistically significant (p = 0.1060).

Appendix Table 10.1.1.n Applicant's Analysis: Event rate of heavy drinking adjusted for baseline percent heavy drinking – ALK21-003

Analysis	Hazard ratio (p-value)	
	190-mg vs. placebo	380-mg vs. placebo
Stratified by 8 strata	0.861 (0.1060)	0.748 (0.0047)
Stratified by 7 strata	0.861 (0.1055)	0.737 (0.0029)
Unstratified	0.89. (0.2396)	0.759 (0.0104)

(Source: Applicant's Table 12, Clinical Study Report ALK21-003, P. 60)

FDA Requested Analyses

a) Responder Analysis

Alkermes conducted a responder analysis using different definitions (or categories) of a treatment responder. Response (or treatment success) was based on the extent to which patients could abstain from heavy drinking, where heavy drinking was defined as ≥ 5 drinks/day (men)

and ≥ 4 drinks/day (women). The monthly proportion of responders in each treatment group was calculated, and the proportions in the Medisorb Naltrexone groups compared to those in the pooled placebo group. The results are shown below:

Appendix Table 10.1.1.o Applicant's Analysis: Responder Rates – ALK21-003

Post-Baseline[1] Heavy Drinking Days per Month[2]	N(%) All	Placebo	190mg	380mg	P-Value* 190mg vs Placebo	380mg vs Placebo
All Subjects	N=611	N=204	N=206	N=201		
0	86 (14%)	23 (11%)	29 (14%)	34 (17%)	0.3938	0.1026
0-1	165 (27%)	44 (22%)	53 (26%)	68 (34%)	0.3217	0.0058
0-2	205 (34%)	56 (27%)	68 (33%)	81 (40%)	0.2205	0.0063
0-3	248 (41%)	68 (33%)	83 (40%)	97 (48%)	0.1442	0.0022
0-4	289 (47%)	84 (41%)	95 (46%)	110 (55%)	0.3133	0.0063

[1] Drinking data up to 30 days after the last dose.
[2] Heavy Drinking Days per Month = (Percent Heavy Drinking Days*30.4)/100.
* Chi-Square test.

(Source: Applicant's Table 25, Clinical Study Report ALK21-003, P. 92)

REVIEWER COMMENT:
The table above presents response rates on an "average number of heavy drinking days per month" basis, and shows the proportion of patients in each treatment arm that met varying cut-offs of monthly average number of heavy drinking days. This analysis did not require that patients never exceed the specified number of heavy drinking days in a given month; instead, all of the patients' heavy drinking days during the observation period were divided by 30 to calculate an "average monthly number of heavy drinking days."

The difference in the proportions of responders between the Medisorb Naltrexone 190-mg and placebo groups was numerically small and not statistically different at any definition of treatment success (i.e. cut-off for average number of heavy drinking days per month).

While there were more Medisorb Naltrexone 380-mg patients (17%) than placebo patients (11%) who showed a sustained absence of heavy drinking over the treatment period (i.e. 0 average monthly heavy drinking days), this difference was not statistically significant. Among persons who averaged up to 1 heavy drinking day per month (i.e. up to 6 heavy drinking days, on average, during the treatment period), the difference between the Medisorb Naltrexone 380-mg and placebo groups was numerically large and reached statistical significance. Similar results were observed at the higher cut-offs of monthly average number of heavy drinking days.

Although these findings may suggest a beneficial treatment effect, it is important to keep in mind that the results of the Project MATCH and NAS re-analyses showed a greater

likelihood of adverse drinking-related consequences when patients display drinking patterns other than a sustained absence of heavy drinking over the course of therapy. Therefore the most relevant results of this analysis are the results of the first row in the table ("0 post-baseline heavy drinking days per month"): a numerically small and statistically non-significant difference between Medisorb Naltrexone 380-mg and placebo with respect to the proportion of patients who averaged no heavy drinking days each month.

Another critical limitation of the Applicant's analysis is that it is based on observed data only. No imputations were made for missing data, including data missing following premature discontinuation from the trial.

Responder analysis – Cumulative plots of per-subject heavy drinking rates
Alkermes plotted cumulative distributions of percentage of heavy drinking days for the treatment groups pre-study and on during the study. The graphs show that prior to treatment, both the placebo and the Medisorb Naltrexone patients had similar frequencies of heavy drinking days. Following treatment, all groups had a considerable decrease in the proportions of reported heavy drinking days. However, there was not much difference between the placebo and 190-mg groups.

Appendix Figure 10.1.1.i: Cumulative distribution per-subject heavy drinking rate (Medisorb Naltrexone 190 mg vs. placebo)

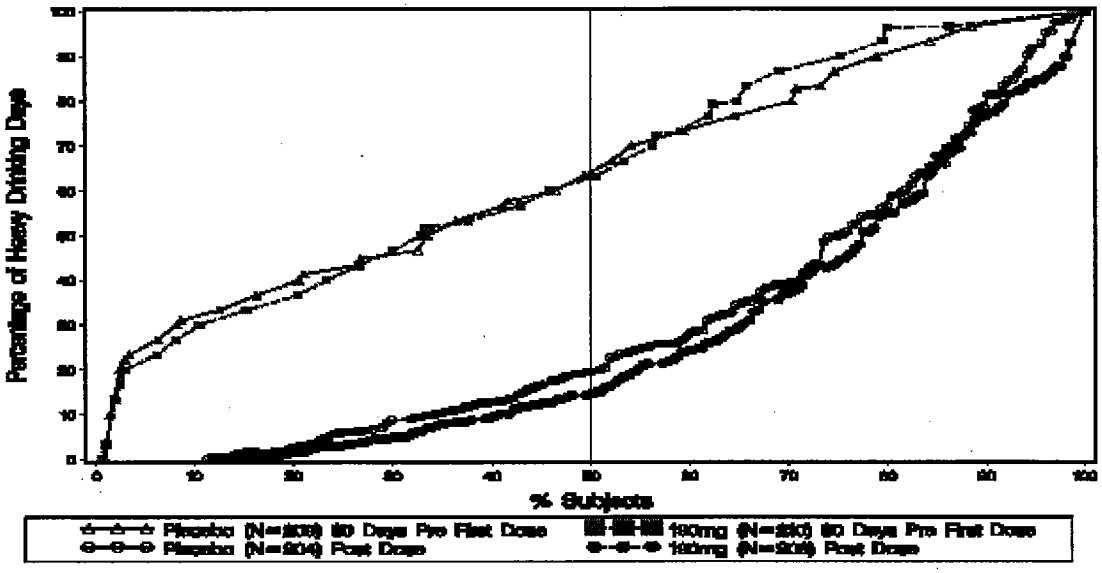
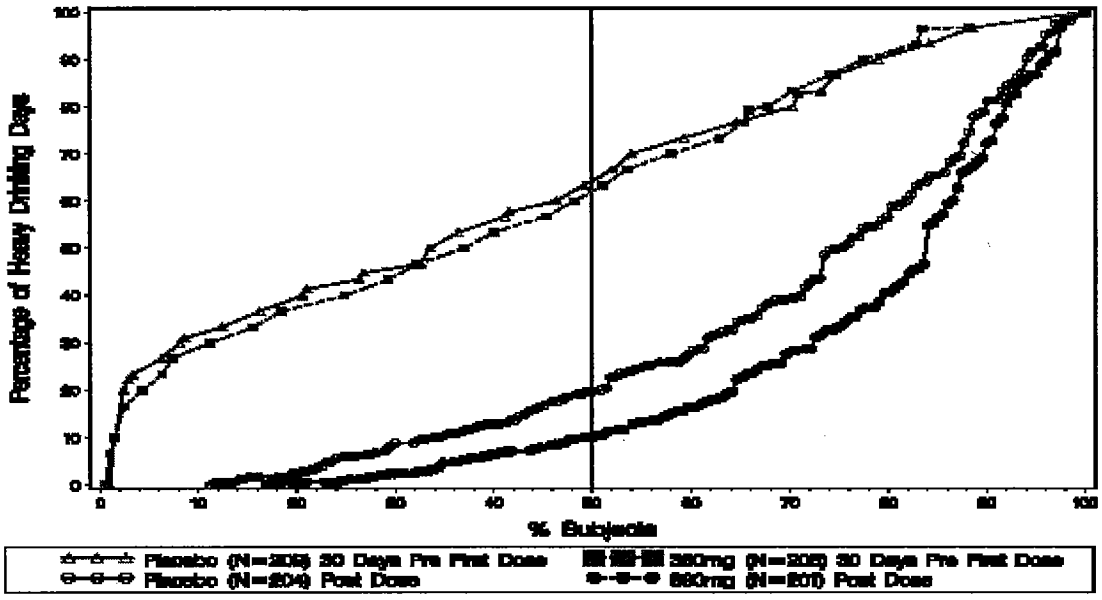


Figure 7: Cumulative Distribution: Per-Subject Heavy Drinking Rate (Medisorb Naltrexone 190 mg vs Placebo)
(Source: Applicant's Figure 7, Clinical Study Report ALK21-003, P. 71)

On the other hand, at the end of the treatment period, the proportion of Medisorb Naltrexone 380-mg patients who reported heavy drinking days was substantially lower than the placebo

group. For example, approximately 11% of patients in the placebo group reported zero heavy drinking days, compared to almost 17% of patients in the 380-mg group.

Appendix Figure 10.1.1.ii: Cumulative distribution per-subject heavy drinking rate (Medisorb Naltrexone 380 mg vs. placebo)



b) Event rate of drinking above the NIAAA derived "safe" level (≥ 1 drink/day (women) and ≥ 2 drinks/day (men)) over the 24-week period

The Division requested that the Alkermes conduct this analysis as an evaluation of the relevance of a statistically significant finding with respect to any observed differences in the event rate of heavy drinking.

Alkermes found that, without stratification for gender, lead-in drinking, and treatment goal, there was no statistically significant difference between either of the Medisorb Naltrexone groups and the pooled placebo group, with respect to the event rate of drinking above the NIAAA "safe" level.

The Applicant attempted to determine whether patients' pre-randomization drinking patterns influenced this result. Patients were sub-categorized according to whether they were abstinent from any drinking in the 4- and 7- days prior to randomization/initiation of study treatment. For both the 190-mg and the 380-mg groups, prior abstinence (for either 4 or 7 days) was associated with a considerable decrease in the event rate of drinking above the NIAAA "safe" level.

REVIEWER COMMENT: These results should be interpreted with caution due to the small numbers of patients in these groups.

Subgroup	Placebo, N	190 mg, N	380 mg, N
Abstinent 4 days pre randomization	27	26	27
Abstinent 7 days pre randomization	18	17	17

Appendix Table 10.1.1.p Applicant's Analysis: Event rate of drinking above the NIAAA-derived 'safe' drinking level – ALK21-003

Analysis*	Vivitrex 190-mg vs. 2-mL placebo			Vivitrex 380-mg vs. 4-mL placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Unstratified	-0.047	0.954 (0.809,1.126)	0.5801	-0.105	0.901 (0.759,1.068)	0.2295
Abstinent 4 days prior to randomization	-1.048	0.251 (0.152,0.808)	0.0128	-1.202	0.200 (0.142, 0.626)	0.0017
Abstinent 7 days prior to randomization	-1.820	0.160 (0.049,0.522)	0.0024	-1.428	0.240 (0.085,0.680)	0.0072

* Not adjusted for baseline percent heavy drinking
(Source: Applicant's Tables 14.2.21.1, 14.2.21.2, and 14.2.21.3, Demographic Data Summary Figures and Tables, Clinical Study Report ALK21-003, P. 238-240)

c) Event rate of any drinking over the 24-week period

The Division also requested that the Applicant calculate the event rate of any drinking, regardless of quantity. Alkermes found that, in the overall population, there was no significant difference in the event rate of any drinking between either Medisorb Naltrexone dose and the pooled placebo group. After reanalyzing the data based on pre-randomization drinking behavior, the Applicant showed that for both the 190-mg and the 380-mg groups, prior abstinence was associated with a considerable decrease in the event rate of any drinking.

Appendix Table 10.1.1.q Applicant's Analysis: Event rate of *any* drinking – ALK21-003

Subgroup	Hazard ratio (p-value)	
	190-mg vs. placebo	380-mg vs. placebo
Overall	0.982 (0.08041)	0.959 (0.5811)
Abstinent during the 4 days prior to randomization	0.362 (0.0056)	0.323 (0.0008)
No lead-in drinking (abstinent during the 7 days prior to randomization)	0.205 (0.0018)	0.295 (0.0079)

(Source: Applicant's Table 30, Clinical Study Report ALK21-003, P. 98)

Secondary Efficacy Analyses

a) Percent days abstinent

Using a last observation carried forward (LOCF) imputation strategy for missing data, the Applicant calculated the each group's percent days abstinence per month. Alkermes found that at baseline, the median percent days abstinent at baseline were 19.2%, 16.7%, and 16.7% for the placebo, 190 mg, and 380 mg groups, respectively. There were no statistically significant

differences among groups at baseline. There were no statistically significant differences between placebo and the 380 mg group or placebo and the 190 mg group at any time in the study. At 30 days post-6th dose, the median percent days abstinent increased to 52.4%, 57.0%, and 52.5% for the placebo, 190 mg, and 380 mg groups, respectively.

b) Time to relapse to drinking

Alkermes also compared the time (days) to relapse to any drinking, heavy drinking, and drinking above the NIAAA "safe" level across the treatment groups. However, as had previously been communicated, the Division does not consider endpoints that rely on time to an initial event to be clinically relevant. This is because the intention of alcohol treatment is not to delay drinking, but to lead to discontinuation or a clinically meaningful reduction of drinking.

10.1.2 Protocol ALK 21-003-EXT

This study is complete.

Title: A multi-center, double blind, extension of Alkermes Study ALK21-003 to evaluate the long-term safety of Medisorb

Objective:
Primary: To evaluate the long-term safety of repeat IM injections of Medisorb Naltrexone administered every 4 weeks.

Secondary: To monitor outcome measures related to drinking activity, social functioning, and healthcare utilization over the treatment period.

Study Description:
This was a multi-center, double blind extension of the efficacy trial ALK21-003. Study ALK21-003 was a 6-month, randomized, double-blind, three-arm, parallel group, placebo-controlled study of Medisorb Naltrexone (190 mg or 380mg q 4 weeks) vs. placebo in 624 alcohol-dependent patients.

In ALK21-003-EXT, 332 alcohol-dependent patients were treated with Medisorb Naltrexone (190mg or 380mg IM) every 4 weeks for 52 weeks beyond their participation in ALK21-003. Therefore, subjects who successfully completed both ALK21-003 and ALK21-003-EXT were administered a total of 19 injections over 1 year, and subjects who received placebo in ALK21-003 were given 13 doses of active drug in the extension study. Subjects administered active drug in ALK21-003 continued on the same dose of Medisorb Naltrexone. Thus, total drug exposure ranged between 28 - 76 weeks. Receipt of psychosocial support therapy (BRENDA) was voluntary.

The primary outcome was the incidence of adverse events. Secondary outcomes included alcohol consumption, social functioning, physical exam findings, injection site assessment, and changes in laboratory values.

Number of subjects: A total of 332 subjects (88% of those eligible) entered this extension study. At least 6 injections were administered to 212 of these subjects (64%), and 148 subjects (45%) completed the study

Study results: Data from this trial were included in the Integrated Summary of Safety.

10.1.3 Protocol ALK 21-010

This study is ongoing.

Study Title: A Multi-Center Extension of Alkermes Study ALK21-003-EXT to Evaluate the Long-Term Safety of Medisorb Naltrexone

Objectives:
Primary Safety Objective: To further evaluate the long-term safety of repeat intramuscular (IM) injections of Medisorb Naltrexone (190 and 380 mg) administered every 4 weeks to alcohol dependent adults.

Secondary Objectives: To monitor measures related to social functioning and healthcare utilization

Study Design: This is a multi-center extension of Alkermes studies ALK21-003 (the efficacy study) and ALK21-003-EXT (the first extension of the efficacy study). Subjects who successfully completed study ALK21-003-EXT are eligible to enroll.

Subjects are given monthly IM injections of Medisorb Naltrexone. Subjects continue to receive the same dose administered in ALK21-003-EXT (i.e., Medisorb Naltrexone 190 mg or 380 mg). The planned duration of ALK21-010 is 3.5 years or until the study is discontinued.

Safety evaluations include assessment of adverse events (AEs), injection sites, vital signs, laboratory test results (hematology, biochemistry, and urinalysis), electrocardiogram (ECG) findings, and physical examination results. Additional endpoints include self-reported social functioning and healthcare utilization as determined by subject-completed questionnaires.

Number of subjects: As of the original NDA data cut-off date, 99 subjects were enrolled, all of whom received study drug. One subject has completed the study, 8 subjects have discontinued, and 90 are continuing.

Study results: Interim data were available at the time of NDA submission, and these were included in the Integrated Summary of Safety.

10.1.4 Protocol ALK 21-006-EXT

This trial had not been initiated at the time of NDA submission.

Title: "An open-label, multi-center study to evaluate the long-term safety of Medisorb Naltrexone"

Objective:
1. To further evaluate the long-term safety of repeat intramuscular (IM) injections of Medisorb Naltrexone in patients with alcohol and/or opiate dependence
2. To monitor measures related to social functioning, healthcare utilization, and drinking behavior

Study Design:
- Open-label, repeat dose, safety study
- 18 sites
- Treatment duration: 3 years
- Population: N = 200 subjects with alcohol and/or opiate dependence
- Medisorb Naltrexone dose (IM, dorso-gluteal region): 380 mg IM Q 4 weeks

Key Inclusion Criteria:
1. Completion of study ALK21-006, or other qualifying trial of Medisorb Naltrexone. Patients must have received all previously scheduled doses.
2. Females of childbearing potential: approved contraception during the study and for 1 month following the last dose

Key Exclusion Criteria:
1. Premature discontinuation of study drug in a previous Medisorb Naltrexone trial
2. Pregnancy
3. Any finding that, in the view of the PI, would compromise the patient's ability to complete the study

Prohibited medications:
Acamprosate, disulfiram, oral naltrexone, methadone, levomethadyl acetate/LAAM, and buprenorphine. Prescription opiates are permitted only when clinically necessary.

Conduct of Study:
Visit 1/Enrollment
Study enrollment coincides with the final visit of ALK21-006 or any other qualifying Medisorb Naltrexone trial. The end-of-study and the enrollment/Visit 1 procedures are combined. Patients who provide informed consent undergo physical examination including vital signs and assessment of the injection site, as well as laboratory testing, and an ECG. Laboratory tests are hematology, blood chemistry with LFTs, urinalysis, and serum pregnancy. The previous 30-days' drinking history is determined using the TLFB method, and subjects complete questionnaires regarding health status, social functioning, and healthcare utilization. Any AEs

and concomitant medications are reviewed. Prior to dosing with Medisorb Naltrexone, patients must have a urine toxicology test that is negative for opiates. If more than 6 weeks have lapsed between Medisorb Naltrexone doses, a urine drug test must be conducted. A naloxone challenge test may be administered in cases where recent opioid use is suspected. Naloxone will not be administered to patients with clinical signs or symptoms of opioid withdrawal or whose urine contains opioids.

Monthly visits, Termination visit
These visits comprise a physical exam with vital signs, injection-site examination, urine pregnancy testing, urine toxicology testing, AE assessment, and recording of concomitant medications.

Every 6 months
Laboratory testing

Every 12 months, Termination visit
ECG, drinking history over the previous 30 days (TLFB method), Social Functioning and Healthcare Utilization questionnaire, SF-36 questionnaire

Statistical Analysis:
Summary descriptive statistics will be provided for all variables. All patients who receive at least 1 dose of study drug will be included in the safety analysis.

Study results:
The study had not been initiated at the time of NDA submission, therefore there are no results to report.

10.1.5 Protocol ALK21-004

See Section 7.1.12.

10.1.6 Protocol ALK21-006

See Section 7.1.12.

10.2 Patient narratives: Deaths

Subject ALK21-003-224-012/AEM – Completed suicide
This was a 56-year-old male with alcohol dependence who was enrolled in study ALK21-003. Past medical history was notable for depression, suicidal ideation (1990's), and treatment with bupropion. Medisorb Naltrexone 190mg was initiated on 3 July 2002 and the patient was treated with a total of 5 doses, the last dose given on [redacted] At that time, the patient was evaluated for major depression and was started on sertraline 50 mg/d. The patient discontinued sertraline on November 2nd, because he felt better. On 18 December 2002, the patient was evaluated by study staff and was noted to be more depressed. The patient was started on bupropion 100 mg BID and began outpatient therapy. The patient attended his follow-up visit on 27 December 2002. On [redacted] the patient committed suicide by stepping in front of a train. The time between the last dose of study drug and the patient's death was approximately 73 days.

Subject ALK21-010-214-008 - Completed suicide
This was a 52-year-old Caucasian male with a medical history of depression and alcohol dependence. The first dose of study drug (Vivitrex, 190 mg) was administered on [redacted] and the 33rd dose of study drug on 02 March 2005. On [redacted], the subject self-inflicted a fatal gunshot wound to the head. It was noted that several psychosocial stressors precipitated the subject's suicide. The interval from the first dose of study drug until the onset of this AE was 952 days.

Subject ALK21-003-214-019/RWN - Homicide
This was a 49-year-old male with alcohol dependence who enrolled in ALK21-003. His medical history was significant for hypertension, blackouts when drinking, and depression. The subject received his first and only dose of Medisorb Naltrexone 190 mg on [redacted] The patient was last seen in the clinic on 31 December 2002. On [redacted] he state police found the subject deceased in his apartment. The medical examiner determined that death occurred on [redacted], 32 days after the first dose of study drug. Cause of death was subdural and subarachnoid hemorrhage due to blunt impact injury of the head, and the death was ruled a homicide. The death certificate and autopsy reports were requested, but were not made available to the Applicant.

> REVIEWER COMMENT: Alkermes listed the patient's disposition status as "withdrawn due to AE." However, the patient discontinued the study not because of death, but for unknown reasons and the patient was lost to follow-up. Therefore the patient's disposition is miscoded.

Subject ALK21-003-EXT-215-009/GDF – Pancreatic cancer
The patient was a 67-year-old male with alcohol dependence who was enrolled in ALK21-003-EXT at the time of his death. His medical history was significant for peptic ulcer disease, gallstones, anemia, lymphadenopathy, and renal insufficiency. The patient had previously been enrolled in ALK21-003 and assigned to Medisorb Naltrexone 380 mg. The patient's first dose of in the extension study was Medisorb Naltrexone 380 mg, administered on [redacted]

Approximately 2 weeks later [redacted], the patient presented to the hospital for progressive abdominal pain, jaundice and diarrhea. Laboratory testing was significant for elevated LFTs (direct bilirubin 2.9 mg/dL, total bilirubin 3.8 mg/dL, alkaline phosphatase 823 U/L, AST 97 U/L, ALT 142 IU/L, and GGT 822 U/L) and normal pancreatic enzymes. An abdominal ultrasound revealed one hepatic mass and one pancreatic mass with associated marked biliary tree and gallbladder dilation. A biopsy confirmed the presence of pancreatic cancer. The patient discontinued the trial on January 7 after having received a total of 7 doses of Medisorb Naltrexone 380 mg. The patient died on [redacted], approximately 9 weeks after the last dose of study drug.

> REVIEWER COMMENT: The patient narrative states that the patient withdrew consent for study participation due to the pancreatic cancer. However, the CRF shows the reason for study termination as being occurrence of a serious adverse event.

Subject ALK21-006-239-012/R-M – Coronary atherosclerosis
This was a 53-year-old female who enrolled in ALK21-006 and, at screening, was identified as having only alcohol dependence. She had previously undergone alcohol detoxification in July 2003. Medical history also included hypertension, depression, and anxiety. Her first dose of study drug (Vivitrex suspension 380 mg) was given on 18 September 2003. She received 9 doses of Vivitrex, with the last dose given on 15 June 2004. O[redacted] she presented to the emergency department with a 2 day history of decreased appetite and abdominal pain. Clinical examination was notable for the following:

CO_2 saturation	18.8%				
Oxygen saturation	359.6 %		O_2 saturation later dropped from 95% to 59%		
Chemistry	Na =130	K =5.9	Cl = 91	CO = 5	BUN 26
	creat 4.0	Glucose 19 mg/dl	CPK = 686	troponin 0.10	AST 5591
	ALT 3859	CK isoenzyme 15	Blood alcohol 4.73 mg/dl		

The patient experienced extreme desaturation and advanced cardiac life support efforts were unsuccessful. The patient died that same day. Autopsy was significant for cerebral swelling; pulmonary edema and consolidation, small hydrothoraces and hemohydroperitoneum, mild cardiomegaly with left ventricular dilatation; atherosclerosis both the aorta and coronary arteries. The medical examiner attributed the cause of death to complications of acute and chronic substance abuse with the contributory cause being coronary atherosclerosis.

10.3 Total SAEs, excluding alcohol-related SAEs

SOC	PT	All subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		Medisorb Naltrexone 380 mg N = 576		Oral NTX N = 65		Placebo N = 214	
		N	%	N	%	N	%	N	%	N	%
Psychiatric disorders	***Total***	***9***	***0.81***	***0***	***0.0***	***6***	***1.03***	***1***	***1.54***	***2***	***0.94***
	Agitation	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Delirium	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Depression	1	0.09	0	0.00	0	0.00	1	1.54	0	0.00
	Drug dependence	2	0.18	0	0.00	2	0.35	0	0.00	0	0.00
	Emotional distress	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Emotional disturbance NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Insomnia	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Psychotic disorder NOS	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
Psychiatric disorders Injury, poisoning and procedural complications	***Suicide-related***	***8***	***0.73***	***0***	***0.0***	***8***	***1.39***	***0***	***0.0***	***0***	***0.0***
	Suicidal ideation	3	0.28	0	0.00	3	0.52	0	0.00	0	0.00
	Suicide attempt	2	0.18	0	0.00	2	0.35	0	0.00	0	0.00
	Non-accidental overdose	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Overdose NOS	2	0.18	0	0.00	2	0.35	0	0.00	0	0.00

Appendix 10.3 Total SAEs, excluding alcohol-related SAEs (continued)

SOC	PT	All subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		Medisorb Naltrexone 380 mg N = 576		Oral NTX N = 65		Placebo N = 214	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	***Total GI***	***7***	***0.63***	***0***	***0.0***	***7***	***1.19***	***0***	***0.0***	***0***	***0.0***
	Constipation	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Gastro-esophageal reflux disease	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Gastrointestinal hemorrhage NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Hemorrhoids	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Perirectal abscess	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Rectal hemorrhage	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Reflux oesophagitis	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
Injury, poisoning and procedural complications	***Any***	***4***	***0.36***	***1***	***0.48***	***2***	***0.34***	***0***	***0.0***	***1***	***0.47***
	Head injury	1	0.09	1	0.48	0	0.00	0	0.00	0	0.00
	Jaw fracture	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Lower limb fracture NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Spinal fracture NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00

Appendix 10.3 Total SAEs, excluding alcohol-related SAEs (continued)

SOC	PT	All subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		Medisorb Naltrexone 380 mg N = 576		Oral NTX N = 65		Placebo N = 214	
		N	%	N	%	N	%	N	%	N	%
Cardiac disorders	***Total***	***3***	***0.27***	***0***	***0.0***	***2***	***0.34***	***0***	***0.0***	***1***	***0.47***
	Atrial fibrillation	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Atrial fibrillation aggravated	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Myocardial infarction	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
General disorders and administration site conditions	***Total***	***3***	***0.27***	***0***	***0.0***	***2***	***0.34***	***0***	***0.0***	***1***	***0.47***
	Chest tightness	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Fatigue	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Injection site necrosis	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
Nervous system disorders	***Total***	***3***	***0.27***	***0***	***0.0***	***3***	***0.51***	***0***	***0.0***	***0***	***0.0***
	Convulsions NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Ischaemic stroke NOS	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Monoplegia	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
Infections and infestations	***Pneumonia***	***3***	***0.27***	***1***	***0.48***	***1***	***0.17***	***0***	***0.0***	***1***	***0.47***
	Interstitial pneumonia,	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
	Pneumonia NOS	2	0.18	1	0.48	0	0.00	0	0.00	1	0.47

Appendix 10.3 Total SAEs, excluding alcohol-related SAEs (continued)

SOC	PT	All subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		Medisorb Naltrexone 380 mg N = 576		Oral NTX N = 65		Placebo N = 214	
		N	%	N	%	N	%	N	%	N	%
Respiratory, thoracic and mediastinal disorders	***Total***	***3***	***0.27***	***0***	***0.0***	***3***	***0.52***	***0***	***0.0***	***0***	***0.0***
	Chronic obstructive airways disease	2	0.18	0	0.00	2	0.35	0	0.00	0	0.00
	Eosinophilic pneumonia acute	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
Musculoskeletal and connective tissue disorders	***Total***	***2***	***0.18***	***0***	***0.0***	***1***	***0.17***	***0***	***0.0***	***1***	***0.47***
	Intervertebral disc herniation	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Lumbar disc lesion	1	0.09	0	0.00	1	0.17	0	0.00	0	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	***Total***	***2***	***0.18***	***1***	***0.48***	***0***	***0.0***	***0***	***0.0***	***1***	***0.47***
	Inflammatory carcinoma of the breast	1	0.09	0	0.00	0	0.00	0	0.00	1	0.47
	Laryngeal cancer NOS	1	0.09	1	0.48	0	0.00	0	0.00	0	0.00

Appendix 10.3 Total SAEs, excluding alcohol-related SAEs (continued)

SOC	PT	All subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		Medisorb Naltrexone 380 mg N = 576		Oral NTX N = 65		Placebo N = 214	
		N	%	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders	*Cervical adenitis*	*1*	*0.09*	*0*	*0.00*	*1*	*0.17*	*0*	*0.00*	*0*	*0.00*
Hepatobiliary disorders	*Cholelithiasis*	*1*	*0.09*	*1*	*0.48*	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*
Pregnancy, puerperium and perinatal conditions	*Abortion missed*	*1*	*0.09*	*0*	*0.00*	*1*	*0.17*	*0*	*0.00*	*0*	*0.00*

10.4 Patient narratives: Suicide-related SAEs – studies of 4-6 months' exposure

Subject ALK21-006-239-016 - Overdose
This is a 38-year-old female with a medical history notable for mixed alcohol and opiate dependence (primary opiate), depression, and anxiety. She was given her first dose of Vivitrex 380 mg on — The most recent dose of Vivitrex prior to the SAE was administered on 04 December. On — , the subject presented for voluntary hospitalization after ingesting 5 Ativan tablets the day before. Although she denied any suicidal/homicidal ideation or audio/visual hallucinations, she did state that she wanted to "get away from sad feelings." Her hospital course was uneventful and she was discharged on — The interval from the first dose of study drug until the onset of this SAE was 86 days. The subject continued in study.

Subject ALK21-006-245-019/ — - Suicidal ideation
This is an 18-year-old male with opiate dependence and depression whose first and only dose of study drug (Medisorb Naltrexone, 380 mg) was administered on — The subject was admitted to the hospital on — 37 days after the first dose of study drug) after expressing suicidal ideations and attempting to jump from a second-story window. The subject had recently been taking cocaine and heroin. The SAE resolved and the subject was discharged on — . The subject discontinued study participation in February 11 2004.

Subject ALK21-006-245-032/ — Overdose
This is an 18-year-old male with opiate dependence and history of suicidal ideation. His first dose of Medisorb Naltrexone 380 mg was given on 21 December 2003. On — the subject was admitted for presumed drug overdose and a decreased level of consciousness. He reportedly took 4 Haldol® (haloperidol) along with 3 Xanax® (alprazolam). Several days prior to admission, he had made several references to dying. He was discharged two days after admission and continued study participation.

Subject ALK21-006-250-019/ — Suicidal ideation
This is a 33-year-old female with alcohol dependence, depression and anxiety. She received her first dose of Vivitrex (380 mg) on 18 December 2003. The subject was admitted to the hospital in — for an SAE of suicidal ideation, and was discharged on — No action was taken with the study drug, and the subject continues in the study.

Subject ALK21-006-252-006/ — - Suicide attempt
This is a 33-year-old male with alcohol dependence who received his first dose of Vivitrex (380 mg) on — On — 73 days after his first dose, the subject ingested approximately 50 Gabitril 12-mg tablets and approximately one-half gallon of vodka with the intention of committing suicide. He was found unconscious, admitted to the hospital, and then discharged on — No action was taken with the study drug, and the subject continued in the study until an exacerbation of alcohol dependence, after which he was lost to follow-up.

Subject ALK21-006-253-004 — Suicide attempt
This 41-year-old female with opiate dependence and bipolar disorder received her only dose of Vivitrex 380-mg on —. On — (approximately 26 days later), the subject was admitted to the hospital on for a suicide attempt (she cut both wrists). No further details were available at the time of data cutoff. Study participation was discontinued on 7 November.

Subject ALK21006-232-001 – Depression
This is a 41-year-old male with a history of alcohol dependence, depression, and suicidal ideation. He was randomized to treatment with oral naltrexone 50 mg/day, and took his first dose on — Concomitant medications included Celexa® (citalopram). On —, 31 days after the first dose of study drug, the subject was admitted to the hospital for exacerbation of alcohol dependence with major depression. During the hospitalization, the subject was treated with oral naltrexone. Also, he had suicidal ideations, but these which ceased prior to discharge on — The subject discontinued from the study on 30 September 2003.

Subject ALK21-006-252-001 – Non-accidental overdose
The subject is a 24-year-old female with a history of opiate dependence, bipolar disorder, depression, anxiety, and panic attack. She was given her first dose of Vivitrex 380 mg on 31 October 2003. The most recent dose of Vivitrex prior to the SAE was administered on 10 March 2004. On 13 April 2004, 166 days after her initial dose, the subject reported taking an intentional overdose on Gabitril 12 mg tablets (quantity unknown) to calm her down and go to sleep after she had an argument with her boyfriend. The subject insists that she had no intention of committing suicide, however during a study visit on 14 April 2004, a mental status evaluation revealed an increase in depressed mood and anxiety. Study drug administration was not interrupted during this event and the subject continued study participation.

10.5 Patient Narratives: SAEs in studies of > 6 months' exposure

Subject ALK21003-210-004 – Acute hepatitis
This is a 47-year-old male with a medical history of hepatitis C infection, active polysubstance abuse (alcohol, heroin, cocaine, marijuana), and depression with 3 previous suicide attempts. The subject completed ALK21-003 during which he was treated with 190-mg Medisorb Naltrexone. He received the first extension-study dose (190 mg) on 30 December 2002.

On 27 April 2003, after a period of reduced alcohol consumption, the subject began a period of heavy drinking. On — four days after his sixth extension-study dose (Dose 12 overall), the subject was admitted to the hospital with a 4-day history of not eating, mid-epigastric, right upper quadrant pain. He also reported taking 2 Vicodin® (hydrocodone/acetaminophen) 3 days prior to admission, after which he vomited (clear vomit) approximately 20 times. Hospital examination was significant for hepatomegaly and elevated LFTs (see table). The patient was diagnosed with acute hepatitis, was treated, and then discharged on —. No further doses were administered, and the subject was discontinued from the study on 04 June 2003 due to the SAE of acute hepatitis.

Table: Chronology and Liver Function Test Results

	ALT (U/L)	AST (U/L)	GGT (U/L)	Total bilirubin (mg/dL)	PT (sec)
Week 24/Dose 6 Last wk of study 003	71	32	94	0.9	-
— Dose 12 Hospital admission	4450	1609	-	3.2	17.5
— Hospital discharge	112	95	-	1.0	-

REVIEWER COMMENT: It is possible that patient's signs and symptoms of acute hepatitis were due to increased alcohol intake, or the combination of alcohol and the acetaminophen (present in Vicodin). However, the acute hepatitis could also have been due to co-administration of naltrexone, alcohol, and acetaminophen. In addition, the abdominal pain and emesis could possibly be related to opiate withdrawal caused by the Medisorb Naltrexone.

ALK21-003-EXT-214-004- Dehydration (due to protracted emesis)
This is a 43-year-old male with alcohol dependence whose medical history includes depression, and mood disorder. The patient successfully completed ALK21-003 (placebo) and was given his first extension-study dose (Vivitrex 190-mg) on 13 November 2002. The most recent dose prior to the SAE (Dose 12 overall) was given on 14 April. On — the subject was transported to the emergency department because he had not eaten for 8 days, and had been unable to retain fluids for the previous 4 days due to repeated emesis. During the hospitalization, the patient was diagnosed as depressed. He was discharged on —. No action was taken with the study drug, and the subject continued participation in the study.

Subject ALK21-006-231-009, — Dehydration (in the context of protracted emesis)

This is a 38-year-old male with a history of mixed alcohol and opiate dependence (primary opiate) and vertigo with nausea. He received his first dose of study drug (Vivitrex 380-mg) on —. The last dose of study medication before the reported event was on 13 July 2004. On —, 283 days since the 1st dose, the subject presented to the emergency department with new onset of nausea, vomiting, abdominal cramps, myalgias and inability to retain fluids due to vomiting. He had had similar symptoms 2 weeks prior, which resolved with fluids and rest. He was hospitalized the same day and later discharged on — The subject continued to participate in the study and receive study medication.

REVIEWER COMMENT: Since nausea, vomiting, abdominal pain, and decreased appetite are known adverse effects of naltrexone, it is possible that the patients' symptoms were due to Medisorb Naltrexone treatment.

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10.6 Adverse events associated with dropouts

Alkermes queried the count dataset source (*iss_ae.xpt* or *iss_subj.xpt*) to calculate the total number of discontinuations by dataset (Appendix Table 10.6.a).

Appendix Table 10.6.a: Applicant's Analysis: Discontinuations by Datasets

QUERY BY DATA SETS	TOTAL # OF DISCONTINUATIONS
ISS.Subj.xpt	122
ISS.ae.xpt	123*
Total number of unique subjects: ISS.Subj.xpt + ISS.ae.xpt	126† (122[(a)] + 4[(b)])
(a) = 122 subjects considered to be discontinued due to AE's in ISS (b) = 4 subjects not considered to be discontinued due to AE's in ISS ("NO" in Table 4) *Please note that our query to the same database results in 123 discontinuations and not 122. If requested by the Agency, we will resubmit the datasets. †Reconciliation of the databases indicated that there was a difference in reporting between the 2 CRFs for subject discontinuations in 10 subjects. Eliminating for duplicates, a combined total for the number of subjects that discontinued due to AEs comes to 126 subjects.	

The ISS included 122 patients who discontinued treatment due to an AE. However, Alkermes' re-evaluation and comparison of the two datasets found 4 additional patients whose AE caused them to drop out of their respective studies, for a total of 126 dropouts. Alkermes explained that the 4 patients were not included in the ISS for a variety of reasons:

Appendix Table 10.6.b: Applicant's explanation of why four (4) patients were excluded from the ISS

STUDY DISCONTD. FROM	SUBJ #	REPORTED DISCONTINUED DUE TO AE IN THE ISS*	EXPLANATION
ALK21-003	215-029	No	As described in the ALK21-003 clinical study report, subject ALK21-003-215-029 discontinued treatment due to a "not clinically significant injection site reaction" (NCS ISR). In this study, ISRs considered NCS by the investigator were not considered adverse events. As such, the subject was excluded from the AE table, and the subject is not in the ISS_ae dataset.
ALK21-003	214-003	No	This subject's AE (exacerbation of alcoholism) began >42 days after the final dose of study drug had been administered. Based on the data handling rules for this study, AEs occurring >42 days after the last dose were not included when determining subjects who discontinued due to an AE.
ALK21-003	236-014	No	The study discontinuation page for this subject indicated that the subject discontinued due to an AE of lightheadedness. The AE CRF did not indicate discontinued for the action taken. At the time of the data cut, the discrepancy had not been resolved.
ALK21-006	248-017	No	The study discontinuation CRF for this subject indicated that the subject discontinued due to NCS ISRs. As above, because the ISRs were deemed by the investigator to be "not clinically significant", they were not considered AEs. As such, the subject is not identified as discontinued due to an AE in the ISS_ae dataset.

REVIEWER COMMENT:
I do not agree with the Applicant's exclusion of patients whose adverse event was labeled as "not clinically significant" (NCS). Regardless of the investigator's opinion of severity, the AE was considerable enough that the patient chose to discontinue study treatment. Therefore, the two patients who were excluded for NCS ISRs (injection site reactions) should be included in the ISS analysis. Also, with regards to the patient who reported lightheadedness, a discrepancy in the AE and study discontinuation forms of the CRF is insufficient reason to exclude the patient from the ISS.

I am also of the opinion that the patient whose relapse to drinking occurred > 42 days after the last dose (subject ALK21003-214-003) should be counted in the ISS. This patient received his 2nd and final dose of study drug on June 18 2002, and by July 14th had resumed drinking (i.e. demonstration of lack of drug efficacy), which was

within 30 days of his last dose. He did not withdraw from the study until [redacted] when he was hospitalized for detoxification.

Although the Applicant believes Subject ALK21003-214-003 should be excluded from the ISS because his AE occurred > 42 days after the last dose, Alkermes included two other patients with AEs that also occurred more than 42 days after the last injection in the ISS: subjects ALK21003-019 (suicidal ideation, alcohol exacerbation) and ALK21003-21-019 (nausea). Therefore the Applicant's reasoning is inconsistent, and the case of worsened drinking/detoxification should be included in the ISS.

During its review of the discontinuation data, Alkermes noted that 10 patients, including the 4 patients above who were incorrectly excluded from the ISS, had different disposition statuses recorded on the adverse event and study drug summary sheets of the CRFs. The remaining 6 cases are described in the table below:

Appendix Table 10.6.c: Applicant's explanation of differences between ISS_ae SAS datasets, ISS_subj SAS datasets and the ISS

STUDY DISCONTD. FROM	SUBJ #	REPORTED DISCONTINUED DUE TO AE IN THE ISS*	EXPLANATION
ALK21-003	212-006	Yes	Subject ALK21-003-212-006 received placebo in ALK21-003 and Vivitrex 380 mg in ALK21-003-EXT. This subject was incorrectly counted as having discontinued twice (once from each study) in the ISS_ae.xpt dataset. This error has been corrected, and the subject is now identified only once as having discontinued from ALK21-003-EXT due to an AE.
ALK21-003-EXT	217-026	Yes	Subject 217-026 reported an AE in study ALK21-003-EXT with action taken marked 'discontinued'. This AE started during study ALK21-003. The two AE records were collapsed. Originally, this subject was identified in the ISS_ae dataset as discontinued from ALK21-003. This has been corrected, and the subject is now correctly reflected as discontinued from ALK21-003-EXT.
ALK21-006	241-022	Yes	The AE CRF for this subject indicated that the subject discontinued due to an AE of pregnancy. However, the subject's study discontinuation CRF indicated the reason for discontinuation was "lost to follow-up". At the time of the data cut, the discrepancy had not been resolved.

Appendix Table 10.6.c: Applicant's explanation of differences between ISS_ae SAS datasets, ISS_subj SAS datasets and the ISS (continued)

STUDY DISCONTD. FROM	SUBJ #	REPORTED DISCONTINUED DUE TO AE IN THE ISS*	EXPLANATION
ALK21-006	255-033	Yes	The AE CRF for this subject indicated that the subject discontinued due to an AE of weight decrease. However, the subject's study discontinuation visit was not conducted until 9/02/04, the date recorded on the study discontinuation CRF. This subject was active at the time of the data cutoff (8/31/04) and was therefore not identified as discontinued in the ISS_subj dataset.
ALK21-006	236-010	Yes	The AE CRF for this subject indicated that the subject discontinued due to an AE of elevated bilirubin. However, the subject's study discontinuation CRF indicated the reason for discontinuation was "lost to follow-up". At the time of the data cut, the discrepancy had not been resolved.
ALK21-006	236-007	Yes	The AE CRF for this subject indicated that the subject discontinued due to an AE of elevated liver function test results. However, the subject's study discontinuation visit was not conducted until 9/28/04, the date recorded on the study discontinuation CRF. This subject was active at the time of the data cutoff (8/31/04) and was therefore not identified as discontinued in the ISS_subj dataset.

Alkermes also found a discrepancy in the number of discontinuations listed in each dataset: whereas *iss_ae.xpt* showed 122 dropouts, *iss_subj.xpt* showed 123 dropouts (Appendix Table 10.6.d).

Appendix Table 10.6.d: Number of Subjects Identified as Discontinued Due to Adverse Events by SAS Dataset, Study Number, and Study Duration

Study No.	ISS_ae.xpt SAS dataset			ISS_subj.xpt SAS dataset*		
	Studies of 4-6 Months' Duration† (Group 1)	Studies of > 6 Months Duration‡ (Group 2)	Total*	Studies of 4-6 Months' Duration	Studies of > 6 Months Duration	Total
ALK21-002	2	0	2	2	0	2
ALK21-003	57¶	0	57‖	57	0	57
ALK21-003-EXT	0	27	27	0	28	28
ALK21-006	32	5	37	30	5	35
Total	91‖	32	123‖	89	33	122

*We arrive at the same number of patients as that found by the agency when number of patients from the 4-6 month study group (Group 1) and > 6 months study group (Group 2) are combined.
†NDA Reference – Module 2, Section 2.7.4.4.2.1, ISS Table 2.25, Page 91
‡NDA Reference – Module 2, Section 2.7.4.5.2.1, ISS Table 2.48, Page 178
‖One subject is counted twice, in both Group 1 and 2. The subject discontinued after > than 6 months of treatment. If this subject is only counted once (in Group 2), a total number discontinued in study ALK21-003 in Group 1 = 56 subjects and the total number of subjects in all studies of 4-6 month duration = 90 subjects. Thus the total number of subjects discontinued comes to 122 patients in both groups combined (90 + 32).
¶ Subject 214-003 was not included in the ISS_ae.xpt SAS dataset as it was not flagged for inclusion in the 6 month analysis or the > 6 month analysis because the AE leading to discontinuation started >42 days after the final dose of study drug had been administered.

As shown in Appendix Table 10.6.d above, the *iss_ae.xpt* dataset listed 91 subjects who discontinued due to AEs, whereas the *iss_subj.xpt* dataset contained 89 discontinuing patients. Alkermes explained that one patient in the *iss_ae.xpt* dataset was counted twice and that there were therefore 90 patients who withdrew due to an AE . There is therefore concordance between the two datasets and the ISS reflects 122 discontinuations due to AEs. However, the difference in the number of discontinuations by study group persists and is presumably due to inconsistencies in CRF data entry.

Alkermes used the information from *iss_ae.xpt* and *iss_subj.xpt* to generate another dataset (*aediscon.xpt)* which listed (by study number) all subjects who discontinued due to AEs. The information in both datasets was reconciled as much as possible, particularly for the 10 cases in which there was a difference in reporting between the adverse event and study drug summary forms of the CRF. After eliminating for duplicates, the new dataset *aediscon.xpt* contained 126 subjects who discontinued because of an AE (the 122 in the original ISS, and the 4 additional patients previously not included in the ISS).

10.7 Reviewer's Analysis: Changes in LFTs

Appendix Table 10.8.a: Reviewer's analysis: Mean Baseline and Week 24 LFTs – Studies ALK21-003 and ALK21-006

	Baseline								Week 24							
	190-mg		380-mg		Oral		PBO		190-mg		380-mg		Oral		PBO	
Parameter	N	μ	N	μ	N	μ	N	μ	N	μ	N	μ	N	μ	N	μ
AST (U/L)	209	32.7	576	29.0	65	26.9	213	31.5	120	27.7	326	28.4	36	28.7	120	30.5
ALT (U/L)	210	32.9	576	31.4	65	27.9	213	33.7	121	28.2	330	28.9	36	27.4	121	31.9
GGT (U/L)	210	73.5	576	63.9	65	51.6	214	74.6	121	57.2	330	45.7	36	34.9	121	67.7
Bilirubin (mg/dL)	210	0.52	576	0.47	65	0.48	213	0.50	121	0.56	331	0.49	36	0.50	121	0.56

μ= Mean

Appendix Table 10.8.b: Reviewer's analysis: Within-group and between-group differences in LFT values – Studies ALK21-003 and -006

	Within-group differences between the BL and Wk24 values [1]				Between-group differences (active vs. placebo) in the Wk24 values			
	190-mg	380-mg	Oral NTX	PBO	190-mg	380-mg	Oral NTX	PBO
Parameter								
AST (U/L)								
Mean difference [2]	-4.89	0.63	3.11	-1.25	2.78	2.09	1.78	-
95% CI	-8.36,-1.42	-1.38, 2.64	-2.31, 8.53	-4.52, 1.65	-2.10, 7.65	-1.94, 6.12	-5.38, 8.97	-
p-value	0.006	0.536	0.252	0.451	0.264	0.310	0.623	-
ALT (U/L)								
Mean difference [2]	-5.03	-0.84	-0.64	-3.06	3.69	2.95	4.49	-
95% CI	-9.04,-1.03	-2.85, 1.17	-5.00, 3.73	-6.87, 0.75	-1.80, 9.19	-1.59, 7.49	-3.63, 12.60	-
p-value	0.014	0.414	0.769	0.115	0.187	0.203	0.278	-

[1] Matched paired t-test.
[2] Mean difference is based on the values available for the matched pairs only

Appendix Table 10.8.c: Reviewer's analysis: Within-group and between-group differences in LFT values – Studies ALK21-003 and -006 (continued)

	Within-group differences between the BL and Wk24 values [1]				Between-group differences (active vs. placc in the Wk24 values			
	190-mg	**380-mg**	**Oral NTX**	**PBO**	**190-mg**	**380-mg**	**Oral NTX**	
Parameter								
GGT (U/L)								
Mean difference [2]	-14.38	-12.87	-22.5	-6.13	10.43	21.96	32.77	
95% CI	-26.4,-2.4	-18.1,-7.5	-42.9,-2.1	-14.9, 2.67	-7.84, 28.72	6.84, 37.07	5.77, 59.8	
p-value	0.019	< 0.0001	0.0316	0.170	0.262	0.004	0.017	
Bilirubin (mg/dL)								
Mean difference [2]	0.03	0.03	0.05	0.05	0.003	0.07	0.06	
95% CI	-0.02, 0.08	N/A	-0.03, 0.04	0.005,0.10	-0.07, 0.07	0.01, 0.13	-0.04, 0.16	
p-value	0.195	0.050	0.186	0.0281	0.926	0.019	0.242	

[1] Matched paired t-test.
[2] Mean difference is based on the values available for the matched pairs only

Appendix Table 10.8.d: Shift table for AST – Studies ALK21-003 and ALK21-006

			Week 24, N (%)		
	Treatment group	**Baseline**	**N**	**H**	**H3**
AST	190 mg	N	100 (70)	6 (4)	0 (0)
	Baseline, N = 210	H	21 (15)	13 (9)	2 (1)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)
AST	380 mg	N	243 (75)	18 (6)	3 (1)
	Baseline, N = 576	H	30 (9)	29 (9)	3 (1)
	Week 24, N = 330	H3	0 (0)	0 (0)	0 (0)
AST	Oral NTX 50 mg	N	28 (78)	3 (8)	0 (0)
	Baseline, N = 65	H	2 (6)	2 (6)	1 (3)
	Week 24, N = 36	H3	0 (0)	0 (0)	0 (0)
AST	Placebo	N	80 (67)	13 (11)	1 (1)
	Baseline, N = 214	H	12 (10)	13 (11)	1 (1)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)

N = normal; H = high; H3 = 3x ULN
Adapted from Applicant's Appendix Table 2.7.4.26, Summary of Clinical Safety)

Appendix Table 10.8.e: Shift table for ALT – Studies ALK21-003 and ALK21-006

			Week 24, N (%)		
	Treatment group	**Baseline**	**N**	**H**	**H3**
ALT	190 mg	N	84 (69)	6 (6)	0 (0)
	Baseline, N = 210	H	22 (18)	8 (7)	1 (1)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)
ALT	380 mg	N	239 (72)	55 (14)	4 (1)
	Baseline, N = 576	H	37 (11)	30 (9)	5 (2)
	Week 24, N = 330	H3	0 (0)	0 (0)	0 (0)
ALT	Oral NTX 50 mg	N	31 (78)	4 (10)	1 (3)
	Baseline, N = 65	H	3 (8)	1 (3)	0 (0)
	Week 24, N = 36	H3	0 (0)	0 (0)	0 (0)
ALT	Placebo	N	80 (66)	8 (7)	1 (1)
	Baseline, N = 214	H	18 (15)	14 (12)	0 (0)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)

Adapted from Applicant's Table 2.30, Summary of Clinical Safety, P. 121-125

Appendix Table 10.8.f: Shift table for GGT – Studies ALK21-003 and ALK21-006

			Week 24, N (%)		
	Treatment group	**Baseline**	**Normal**	**High**	**3x ULN**
GGT	190 mg	N	115 (60)	6 (3)	0 (0)
	Baseline, N = 210	H	21 (11)	30 (16)	3 (2)
	Week 24, N = 121	H3	2 (1)	8 (4)	8 (4)
GGT	380 mg	N	225 (68)	6 (2)	1 (<1)
	Baseline, N = 576	H	37 (11)	41 (12)	3 (1)
	Week 24, N = 330	H3	2 (1)	6 (2)	9 (3)
GGT	Oral NTX 50 mg	N	25 (69)	0 (0)	0 (0)
	Baseline, N = 65	H	6 (17)	3 (8)	0 (0)
	Week 24, N = 36	H3	0 (0)	2 (6)	0 (0)
GGT	Placebo	N	63 (52)	9 (7)	0 (0)
	Baseline, N = 214	H	16 (13)	21 (17)	2 (2)
	Week 24, N = 121	H3	0 (0)	3 (2)	7 (6)

Adapted from Applicant's Table 2.30, Summary of Clinical Safety, P. 121-125

Appendix Table 10.8.g: Shift table for Total bilirubin – Studies ALK21-003 and ALK21-006

			Week 24, N (%)*		
	Treatment group	**Baseline**	**N**	**H**	**H3**
Bili	190 mg	N	141 (97)	2 (1)	0 (0)
	Baseline, N = 210	H	0 (0)	2 (1)	0 (0)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)
Bili	380 mg	N	325 (98)	5 (2)	0 (0)
	Baseline, N = 576	H	0 (0)	1 (<1)	0 (0)
	Week 24, N = 331	H3	0 (0)	0 (0)	0 (0)
Bili	Oral NTX 50 mg	N	35 (97)	1 (3)	0 (0)
	Baseline, N = 65	H	0 (0)	0 (0)	0 (0)
	Week 24, N = 36	H3	0 (0)	0 (0)	0 (0)
Bili	Placebo	N	118 (98)	3 (2)	0 (0)
	Baseline, N = 213	H	0 (0)	0 (0)	0 (0)
	Week 24, N = 121	H3	0 (0)	0 (0)	0 (0)

* Percentages are out of the number of subjects with test results at baseline and the Week 24 visit for each treatment group
(Adapted from Applicant's Summary of Clinical Safety, Appendix Table 2.7.4.26)

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10.8 Patient narratives: Non-serious suicide-related AEs

Studies of 4-6 months' duration

Subject ALK21-006-232-001 – Self harm
This is a 41-year-old male with alcohol dependence, received his first dose of study drug, oral naltrexone (50 mg), on 19 August 2003. He has a previous history of suicidal ideation. On August 31, 12 days since the 1st dose, the patient reported an episode of intentional self injury. The subject continued on the study for a short time, subsequently experienced serious exacerbation of alcohol dependence, and then he discontinued participation.

Subject ALK21-006-235-002 – Heroin overdose
This is a 22-year-old male with mixed alcohol and opiate abuse (primary: opiate) who had his first dose of oral naltrexone (50 mg) on 21 August 2003. His medical history includes 2 seizures after taking a combination of LSD, Vicodin® and alcohol. On 24 April 2004, 247 days after the initial dose, the subject overdosed on heroin. He discontinued from the study on 27 April.

Subject ALK21-006-231-008 – Suicidal ideation
This is a 36-year-old male with alcohol dependence who had his first dose of Vivitrex (380 mg) on 23 October 2003. Medical history included major depressive disorder, attention deficit hyperactivity disorder, and nervousness. Prior to the AE, the most recent injection of Vivitrex was on 11 March 2004. On 12 March 2004, 142 days since the 1st dose, the subject reported suicidal ideation which resolved on 23 March. The subject continued participation in the study.

Subject ALK21-006-232-003 – Suicidal ideation
This is a 58-year-old female with alcohol dependence, who had her first injection of Vivitrex 380 mg on 28 October 2003. The subject has a history of depression, and schizophrenia. From 17 to 18 November, approximately 21 days since her 1st injection, she reported suicidal ideation for which hospitalization was not required. The subject continued participation in the study.

Subject ALK21-006-236-006 – Suicidal ideation
This is a 43-year-old male with alcohol dependence, who had his first dose of oral naltrexone (50 mg) on 14 November 2003. The subject's medical history includes HIV positive status, depression, and anxiety. From 19 to 20 November, 5 days following his first injection, the subject had a reported AE of mild suicidal ideation, The AE was considered resolved on 21 November. The subject continued in the study until 06 April 2004, when he was lost to follow-up.

Subject ALK21-006-237-016 – Suicidal ideation
This is a 48-year-old male with alcohol dependence, who received his first injection of Vivitrex 380 mg on 26 January 2004. His medical history includes depression, and anxiety. On 11 February, 17 days following his first injection, he reported intermittent suicidal ideation in connection with drinking. The subject remained in the study, and continued to experience intermittent suicidal ideation primarily in connection alcohol use.

Subject ALK21-006-246-012 – Suicidal thoughts
This is a 29-year-old male with mixed alcohol and opiate dependence. He has a history of major depression and suicidal gestures. He received his first dose of oral naltrexone (50 mg) on 09

October 2003. On 17 November, 39 days since is 1st dose, he reported intermittent suicidal ideation which continued until his withdrawal from the study on 19 February 2004.

Subject ALK21-006-254-006 – Suicidal ideation
This is a 44-year-old female with a history of alcohol dependence and depression. She received the first dose of study drug Medisorb Naltrexone 380 mg on 09 February 2004. Her most recent injection prior to the AE was given on July 15, at which time she described suicidal ideation. The interval from the first dose of study drug until the onset of the suicidal ideation was 152 days. She continued participation in the trial, and the AE was considered resolved on July 15.

Subject ALK21-006-255-004 – Suicidal ideation
This is a 37-year-old female with alcohol dependence with a considerable psychiatric history: depression, suicide attempt, post traumatic stress disorder, detoxification, dysthymia, and anxiety. She was given her first dose of Vivitrex 380 mg on 05 February 2004. Prior to the reported event, the most recent injection of Vivitrex was administered on 05 March. From 18 to 19 March, 43 days since her 1st dose, she experienced intermittent suicidal ideation. The event was considered resolved on 19 March. The subject continued to participate in the study.

Subject ALK21-003-208-024 – Suicidal ideation
This is a 47-year-old female with alcohol dependence, depression and anxiety. She received her first dose Medisorb Naltrexone 190-mg on 17 June 2002. On 10 July, 24 days after her 1st dose, the subject reported suicidal ideation which resolved within 2 days. . The investigator determined that the subject was stable enough to continue in the study and the second dose was given administration of study drug on 16 July. Upon further examination of the subject after the second dose, the investigator judged that the subject should not receive any further injections and she discontinued from the study on 13 August.

Subject ALK21-003-224-019 – Suicidal ideation
This is a 29-year-old male with alcohol dependence. He was given his first and only dose of Medisorb Naltrexone 190 mg on [redacted]. On [redacted] 36 days after the sole dose of study drug, he experienced suicidal ideation and an exacerbation of alcohol for which he was hospitalized. The subject refused any further injections of study drug, and was determined to be lost to follow-up on 21 November 2002.

Subject ALK21-006-233-015 – Sulfuric acid contact
This is a 51-year-old Caucasian male with alcohol dependence and situational depression. The subject enrolled in study ALK21-006 on 21 January 2004. The first dose of Vivitrex 380 mg was administered on 30 January and the fifth dose on 20 May. Approximately 17 days later, on 06 June 2004, the subject experienced a moderate exposure of sulfuric acid to the left side of the neck. The AE resolved on 15 June. He received 8 subsequent doses and completed the study on 15 February 2005.

REVIEWER COMMENT: The patient narrative did not describe how the patient came to be exposed to sulfuric acid, or whether the exposure occurred in the context of a depressive episode. I reviewed the patient's CRF and noted that the Adverse Event sheet indicated that the patient had been depressed, reportedly starting on Jun 15 2004 and that the depression was "continuous." Therefore, it is possible that the patient

had been depressed around the time of the AE, and that the exposure was non-accidental.

Subject ALK21-006-233-017 – Accidental ingestion of GHB
This is a 23-year-old Caucasian female with opiate dependence. She enrolled in study ALK21-006 on 30 January 2004, and the first dose of study drug (Medisorb Naltrexone, 380 mg) was administered on 13 February 2004. On the night of [redacted], GHB was placed in her Gatorade® without her knowledge. The subject visited the emergency room the same night and was released within 3 hours.

Patient narratives: Non-serious suicide-related AEs - >6 months' duration

Subject ALK21-006-231-001/ [redacted] Heroin overdose
This is a 22-year-old female with opiate dependence who had her first dose of Vivitrex 380 mg on 19 September 2003. Medical history included bulimia, bipolar disorder, anxiety, depression, and panic attacks. The interval from the first dose until the onset of this AE (heroin overdose) was 242 days. On 17 May 2004, 242 days since the initial study dose, the patient took an overdose of heroin. No further information was available at the time of data cutoff. The subject discontinued on 28 May 2004 reporting "a return to heroin use."

Subject ALK21-006-235-002 – Heroin overdose
This is a 22-year-old male with mixed alcohol and opiate abuse (primary: opiate) who had his first dose of oral naltrexone (50 mg) on 21 August 2003. His medical history includes 2 seizures after taking a combination of LSD, Vicodin® and alcohol. On 24 April 2004, 247 days after the initial dose, the subject overdosed on heroin. He discontinued from the study on 27 April.

Subject ALK21-006-214-004 – Self injury
This is a 28-year-old male with mixed alcohol and opiate dependence who had his first dose of Vivitrex 380 mg) on 21 January 2004. The most recent injection of Vivitrex prior to this reported AE was administered on 14 July. The interval from the first dose of study drug until the onset of this event was 204 days. On 11 August, the patient reported an event of self-mutilation and a self-inflicted laceration to the right forearm, was reported. Keflex® (cephalexin) was prescribed for the laceration. The subject was discontinued from the study on 11 August 2004 because he was "not motivated for treatment."

10.9 Common Adverse Events (events in ≥ 1% of Medisorb Naltrexone patients)

Appendix Table 10.9

Body system/SOC	Adverse Event	Medisorb Naltrexone								Placebo	
		400-mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440		N = 214	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Nausea	8	32.00	68	33.17	53	25.24	129	29.32	24	11.21
	Vomiting NOS	3	12.00	28	13.66	22	10.48	53	12.05	12	5.61
	Diarrhea [1]	3	12	27	13.17	27	12.85	57	12.95	21	9.81
	Abdominal pain [2]	4	16	23	11.22	23	10.96	50	11.36	17	7.95
	Dry mouth	6	24.00	10	4.88	8	3.81	24	5.45	9	4.21
	Constipation	1	4.00	8	3.90	3	1.43	12	2.73	5	2.34
	Flatulence, bloating, or distension	1	4	7	3.42	1	0.48	9	2.04	2	0.94
	GERD, gastritis, or dyspepsia	0	0.0	7	3.41	5	2.38	12	2.73	12	5.61
Investigations	Abnormal liver function test - Total	3	12	12	5.85	12	5.72	27	6.15	14	6.53
	GGT increased	1	4.00	4	1.95	4	1.90	9	2.05	7	3.27
	AST increased	1	4.00	3	1.46	3	1.43	7	1.59	2	0.93
	Liver function tests NOS abnormal	0	0.00	3	1.46	2	0.95	5	1.14	2	0.93
	ALT increased	1	4.00	2	0.98	1	0.48	4	0.91	2	0.93
	Alkaline phosphatase NOS increased	0	0.00	0	0.00	1	0.48	1	0.23	0	0.00
	Blood bilirubin increased	0	0.00	0	0.00	1	0.48	1	0.23	1	0.47
	Creatine or creatinine phosphokinase increased	1	4	2	0.98	4	1.91	7	1.59	6	2.8
	Eosinophil count increased	0	0.00	2	0.98	1	0.48	3	0.68	1	0.47
	Blood pressure increased	0	0.00	3	1.46	3	1.43	6	1.36	4	1.87
	Weight decreased	0	0.00	3	1.46	3	1.43	6	1.36	1	0.47
	Blood glucose increased	0	0.00	1	0.49	4	1.90	5	1.14	1	0.47

GERD: gastroesophageal reflux disease; SOC: system organ class

[1] Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools

[2] Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower

Appendix Table 10.9:Common Adverse Events (events in ≥ 1% of Medisorb Naltrexone patients) - continued

Body system/SOC	Adverse Event	Medisorb Naltrexone								Placebo	
		400-mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440		N = 214	
		N	%	N	%	N	%	N	%	N	%
Infections and infestations	Upper respiratory tract infection, other [3]	0	0.0	27	13.17	25	11.9	52	11.81	28	13.08
	Pharyngitis [4]	0	0.0	22	10.73	35	16.67	57	12.95	23	10.75
	Influenza	0	0.00	6	2.93	5	2.38	11	2.50	9	4.21
	Gastroenteritis NOS	0	0.0	6	2.93	5	2.38	11	2.5	5	2.33
	Lower respiratory tract infection [5]	1	4.00	5	2.44	8	3.81	14	3.18	5	2.34
	Infection [6]	0	0.0	5	2.44	10	4.78	15	3.42	2	0.94
	Urinary tract infection, kidney infection NOS	0	0.0	3	1.47	2	0.95	5	1.14	1	0.47
	Hepatitis C	0	0.00	1	0.49	1	0.48	2	0.45	0	0.00
	Herpes simplex, herpes zoster	1	4.00	2	0.98	1	0.48	4	0.9	0	0.0
	Cellulitis	0	0.00	0	0.00	1	0.48	1	0.23	0	0.00
Psychiatric disorders	Insomnia, sleep disorder	2	8.00	29	14.15	27	12.86	58	13.19	25	11.68
	Anxiety [7]	2	8.00	24	11.71	16	7.62	42	9.54	17	7.94
	Depression, suicidal ideation	0	0.00	17	8.29	9	4.28	26	5.91	9	4.21
	Libido decreased	1	4.00	11	5.37	3	1.43	15	3.41	2	0.93
	Irritability/anger	1	4.00	10	4.88	7	3.34	18	4.09	5	2.34
	Parasomnias [8]	0	0.00	7	3.41	5	2.38	12	2.73	2	0.93
	Alcoholism, alcohol withdrawal syndr.	1	4	7	3.42	8	3.81	16	3.64	9	4.2
	Euphoric mood, mood swings	0	0.0	4	1.95	2	0.95	6	1.37	0	0.0

[3] Includes the preferred terms: upper respiratory tract infection NOS; laryngitis NOS; sinusitis NOS
[4] Includes the preferred terms: nasophyaryngitis; pharyngitis streptococcal; pharyngitis NOS
[5] Includes the preferred terms: bronchitis NOS; interstitial pneumonia; bronchitis acute NOS; pneumonia NOS
[6] Includes the preferred terms: infection NOS; viral infection NOS; bacterial infection NOS; candidal infection NOS; fungal infection NOS; fungal rash NOS; nail fungal infection; dermatophytosis NOS
[7] Includes the preferred terms: anxiety NEC, anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress disorder; obsessive-compulsive personality disorder
[8] Includes the preferred terms: abnormal dreams; rapid eye movements sleep abnormal

Appendix Table 10.9: Common Adverse Events (events in ≥ 1% of Medisorb Naltrexone patients) - continued

Body system/SOC	Adverse Event	Medisorb Naltrexone								Placebo	
		400-mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440		N = 214	
		N	%	N	%	N	%	N	%	N	%
General disorders and administration site conditions	Asthenic conditions [9]	3	12	47	22.93	40	19.05	90	20.44	26	12.15
	Injection site reaction - Total	5	20	58	28.31	46	21.92	109	24.78	17	7.95
	Injection site pain	4	16.00	24	11.71	19	9.05	47	10.68	12	5.61
	Injection site induration	1	4.00	13	6.34	7	3.33	21	4.77	4	1.87
	Injection site rash	0	0.00	2	0.98	1	0.48	3	0.68	1	0.47
	Injection site pruritus	0	0.00	6	2.93	6	2.86	12	2.73	0	0.00
	Injection site edema	0	0.00	5	2.44	3	1.43	8	1.82	0	0.00
	Injection site inflammation	0	0.00	4	1.95	1	0.48	5	1.14	0	0.00
	Injection site reaction NOS	0	0.00	2	0.98	1	0.48	3	0.68	0	0.00
	Injection site bruising	0	0.00	1	0.49	4	1.90	5	1.14	0	0.00
	Injection site mass	0	0.00	1	0.49	2	0.95	3	0.68	0	0.00
	Injection site burning	0	0.00	0	0.00	1	0.48	1	0.23	0	0.00
	Injection site hypersensitivity	0	0.00	0	0.00	1	0.48	1	0.23	0	0.00
	Chest pain, discomfort, tightness	0	0.0	5	2.44	1	0.48	6	1.37	4	1.87
Injury, poisoning and procedural complications	Injury [10]	2	8.00	20	9.77	28	13.36	50	11.38	23	10.73
	Procedural complications [11]	0	0.0	4	1.96	2	0.95	6	1.37	3	1.4
	Foot, rib, hand fracture	0	0.0	0	0.0	4	1.91	4	0.91	0	0.0
Musculoskeletal and connective tissue disorders	Arthralgia,, arthritis, joint stiffness	1	4	24	11.71	12	5.72	37	8.42	11	5.14
	Muscle cramps [12]	0	0.0	16	7.82	5	2.38	21	4.77	3	1.4
	Pain in limb	0	0.00	13	6.34	2	0.95	15	3.41	6	2.80
	Back pain, stiffness	1	4.00	12	5.86	14	6.67	27	6.14	10	4.68

[9] Includes the preferred terms: malaise , fatigue (these two comprise the majority of cases); lethargy, sluggishness,
[10] Includes the preferred terms: muscle strain; muscle injury NOS; limb injury NOS; injury NOS; back injury NOS; head injury; neck injury; joint sprain; ligament sprain; epicondylitis; road traffic accident; accident at work; whiplash injury; laceration; abrasion NOS; thermal burn; burns second degree
[11] Includes the preferred terms: post procedural pain; post procedural discomfort; needle stick/ puncture
[12] Includes the preferred terms: muscle cramps, spasms, tightness, twitching, stiffness, rigidity

Appendix Table 10.9: Common Adverse Events (events in ≥ 1% of Medisorb Naltrexone patients) - continued

Body system/SOC	Adverse Event	Medisorb Naltrexone								Placebo	
		400-mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440		N = 214	
		N	%	N	%	N	%	N	%	N	%
Musculoskeletal and connective tissue disorders *(contd.)*	Myopathy, muscle fatigue, muscle disorder NOS	0	0.0	4	1.96	1	0.48	5	1.13	0	0.0
	Swelling; peripheral swelling NOS	0	0.0	2	0.98	3	1.43	5	1.13	3	1.4
Skin and subcutaneous tissue disorders	Rash [13]	3	12	12	5.86	10	4.76	25	5.68	8	3.74
	Sweating [14]	0	0.0	7	3.42	8	3.81	15	3.42	4	1.87
	Pruritus NOS	1	4.00	4	1.95	2	0.95	7	1.59	1	0.47
	Contusion, erythema	1	4.00	4	1.95	7	3.34	12	2.72	5	2.34
	Angioedema, urticaria, angioneurotic edema	1	4.00	2	0.98	6	2.85	9	2.05	0	0.0
Nervous system disorders	Headache [15]	9	36	51	24.89	34	16.19	94	21.36	39	18.23
	Dizziness, syncope	4	16	27	13.17	27	12.85	58	13.19	9	4.21
	Somnolence, sedation	3	12	8	3.9	9	4.29	20	4.55	2	0.93
	Hypoesthesia, hypoesthesia oral	2	8.00	10	4.88	7	3.33	19	4.32	8	3.74
	Disturbed attention, mental impairment NOS	0	0.00	5	2.44	1	0.48	6	1.36	0	0.0
	Taste alteration (ageusia, dysgeusia)	0	0.0	4	1.95	0	0.0	4	0.91	2	0.93
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	1	4.00	8	3.90	5	2.38	14	3.18	5	2.34
	Congestion (sinus, nasal), rhinitis	0	0.0	8	3.91	6	2.85	14	3.18	2	0.94
	Cough, throat irritation	1	4.00	5	2.44	3	1.43	9	2.05	7	3.27
	Breathing/respiratory abnormalities [16]	1	4.00	3	1.47	1	0.48	5	1.14	2	0.93
	Eosinophilic pneumonia acute	0	0.00	1	0.49	0	0.00	1	0.23	0	0.00

[13] Includes the preferred terms: rash NOS; rash popular; heat rash
[14] Includes the preferred terms: sweating increased; night sweats; cold sweat
[15] Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches
[16] Includes the preferred terms: dyspnea, wheezing; respiration abnormal NOS

Appendix Table 10.9: Common Adverse Events (events in ≥ 1% of Medisorb Naltrexone patients) - continued

Body system/SOC	Adverse Event	Medisorb Naltrexone								Placebo	
		400-mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440		N = 214	
		N	%	N	%	N	%	N	%	N	%
Metabolism and nutrition disorders	Anorexia, appetite decreased NOS, appetite disorder NOS	5	20	30	14.63	13	6.19	48	10.91	6	2.8
	Appetite increased NOS	1	4.00	4	1.95	3	1.43	8	1.82	2	0.93
Eye disorders	Ocular infections, irritations and inflammations [17]	1	4.00	10	4.89	1	0.48	12	2.73	0	0.0
Reproductive system and breast disorders	Erectile dysfunction NOS [18]	0	0.00	1	0.72	2	1.41	3	1.01	0	0.00
Renal and urinary disorders	Urinary frequency, incontinence; nocturia; polyuria	0	0.0	5	2.45	1	0.48	6	1.37	5	2.34
Cardiac disorders	Cardiac arrhythmia (arrhythmia NOS, extrasystole, palpitations)	0	0.0	2	0.98	2	0.96	4	0.91	0	0.0
Vascular disorders	Hypertension NOS	0	0.0	2	0.98	6	2.85	8	1.81	3	1.4
	Flushing, hot flushes NOS	1	4.00	3	1.46	5	2.38	9	2.04	0	0.0
Immune system disorders	Allergic conditions (hypersensitivity NOS, seasonal allergy)	0	0.0	4	1.95	3	1.43	7	1.59	2	0.94

[17] Includes the preferred terms: conjunctivitis NOS, eye irritation; conjunctival hyperemia; eye inflammation NOS; eye pruritus; eye allergy
[18] N males (400-mg) = 17; N males (380-mg) = 138; N males (190-mg) = 142; N males (all Medisorb naltrexone) = 297; N males (placebo) = 148

The table lists the commonly adverse events that occurred in at least 1% of Medisorb Naltrexone treated patients. Adverse events that were unlikely to have been caused by treatment (e.g. myocardial infarction) or that occurred more frequently in placebo-treated patients are excluded.

10.10 Demographic information for patients in Phase 1-3 trials

(Tables taken from the Applicant's Summary of Clinical Safety, Tables 2.6, 2.7, 2.16, 2.17, 2.40, and 2.41; p. 42-43, 64-65, 157-58)

10.10.1 Phase 1 trials

Table 2.6: Demographic Characteristics of Subjects Participating in Clinical Pharmacology Studies (1-4 months[1] exposure)

		Vivitrex Suspension					
		Placebo		<190 mg		190 mg	
		Alk21-001	Alk21-005	Alk21-001	Alk21-004	Alk21-005	Alk21-009
N		7	6	10	17	12	25
Age (yrs)	N	7	6	10	17	12	25
	Median	26.0	38.0	23.5	42.0	38.0	53.0
	Mean	25.6	35.7	25.4	38.8	36.3	55.6
	SD	3.5	8.8	5.8	8.3	8.8	8.5
	Range	20-31	24-46	19-37	23-50	20-49	43-76
Gender, N(%)	Male	7 (100.0)	3 (50.0)	10 (100.0)	16 (94.1)	6 (50.0)	15 (60.0)
	Female	0 (0.0)	3 (50.0)	0 (0.0)	1 (5.9)	6 (50.0)	10 (40.0)
Race, N(%)	Caucasian	7 (100.0)	0 (0.0)	10 (100.0)	4 (23.5)	2 (16.7)	10 (40.0)
	African American	0 (0.0)	0 (0.0)	0 (0.0)	13 (76.5)	1 (8.3)	0 (0.0)
	Hispanic	0 (0.0)	6 (100.0)	0 (0.0)	0 (0.0)	9 (75.0)	15 (60.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2.7: Baseline Characteristics of Subjects in Clinical Pharmacology Studies (1-4 months[1] exposure)

	Drug	Placebo		Vivitrex Suspension								Oral Naltrexone	
	Unit dose, mg	0		< 190		190		> 190, < 380		380	> 380	50	
	Study No. ALK21-	001	005	001	004	005	009	001	004	005	001	001	005
	Actual Dose(s) Administered			141	75, 150			269	300		530, 784		
	N	7	6	10	17	12	25	10	10	24	15	6	42
Subject Population	Healthy subject	7	6	10	0	12	13	10	0	24	15	6	42
	Mild-moderate hepatic impairment	0	0	0	0	0	12	0	0	0	0	0	0
	Alcohol dependent	0	0	0	0	0	0	0	0	0	0	0	0
	Opiate dependent	0	0	0	0	0	0	0	0	0	0	0	0
	Non-dependent opioid users	0	0	0	17	0	0	0	10	0	0	0	0

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10.10.2 Phase 2 and Phase 3 trials

Table 2.16: Demographic Characteristics: Studies of Dependent Subjects (4-6 Months[1] of Exposure)

		Placebo ALK21-002/ ALK21-003	Vivitrex Suspension 190 mg ALK21-003	380 mg ALK21-003	380 mg ALK21-006	400 mg ALK21-002	380/400 mg Combined	Oral Naltrexone ALK21-006	All Subjects
N Dosed		214	210	205	371	25	601	65	1090
Age (yrs)	N	214	210	205	371	25	601	65	1090
	Median	44.0	44.0	45.0	41.0	43.0	43.0	42.0	43.0
	Mean	44.7	44.6	45.0	40.7	42.8	42.3	40.5	43.1
	SD	10.7	10.8	10.1	11.2	9.4	11.0	11.4	11.0
	Range	21 - 79	19 - 72	21 - 72	18 - 70	27 - 59	18 - 72	21 - 69	18 - 79
Gender, N(%)	Male	148 (69.2)	142 (67.6)	138 (67.3)	233 (62.8)	17 (68.0)	388 (64.6)	42 (64.6)	720 (66.1)
	Female	66 (30.8)	68 (32.4)	67 (32.7)	138 (37.2)	8 (32.0)	213 (35.4)	23 (35.4)	370 (33.9)
Race, N(%)	Caucasian	184 (86.0)	169 (80.5)	172 (83.9)	311 (83.8)	15 (60.0)	498 (82.9)	56 (86.2)	907 (83.2)
	African American	17 (7.9)	17 (8.1)	16 (7.8)	31 (8.4)	2 (8.0)	49 (8.2)	3 (4.6)	86 (7.9)
	Hispanic	7 (3.3)	15 (7.1)	10 (4.9)	21 (5.7)	0	31 (5.2)	4 (6.2)	57 (5.2)
	Other	6 (2.8)	9 (4.3)	7 (3.4)	8 (2.2)	4 (16.0)	19 (3.2)	2 (3.1)	36 (3.3)
	Not collected	0	0	0	0	4 (16.0)	4 (0.7)	0	4 (0.4)

Table 2.17: Baseline Substance Abuse Characteristics: Studies of Dependent Subjects (4-6 Months[1] of Exposure)

		Placebo ALK21-002/ ALK21-003	Vivitrex Suspension 190 mg ALK21-003	380 mg ALK21-003	380 mg ALK21-006	400 mg ALK21-002	380/400 mg Combined	Oral Naltrexone ALK21-006	All Subjects
Number of Subjects Dosed		214	210	205	371	25	601	65	1090
Alcohol Dependent, N		214	210	205	270	25	500	45	989
Opiate/Mixed Dependent, N		0	0	0	101	0	101	20	121
Lead-in Drinking[2], N(%)									
	Yes	190 (90.9)	193 (91.9)	188 (91.7)	220 (63.4)		408 (73.9)	42 (72.4)	833 (81.0)
	No	19 (9.1)	17 (8.1)	17 (8.3)	127 (36.6)		144 (26.1)	16 (27.6)	196 (19.0)

Table 2.40. Demographic Characteristics of Subjects in Studies Longer than 6 Months[1]

		Vivitrex Suspension (mg) ALK21-003-EXT and ALK21-010[2] PBO[3]/190	190/190	PBO/380	380/380	ALK21-006 380	ALK21-006 Oral 50mg	All Subjects
N Dosed		55	102	60	115	204	36	572
Age (yrs)	N	55	102	60	115	204	36	572
	Median	48.0	46.0	44.0	46.0	43.0	42.5	45.0
	Mean	48.7	46.7	44.8	45.8	41.8	42.3	44.5
	SD	10.6	10.4	10.1	9.3	10.8	12.6	10.7
	Range	26 - 79	19 - 72	26 - 73	27 - 70	18 - 70	22 - 69	18 - 79
Gender, N(%)	Male	38 (69.1)	66 (64.7)	43 (71.7)	70 (60.9)	133 (65.2	25 (69.4)	375 (65.6)
	Female	17 (30.9)	36 (35.3)	17 (28.3)	45 (39.1)	71 (34.8	11 (30.6)	197 (34.4)
Race, N(%)	Caucasian	50 (90.9)	83 (81.4)	50 (83.3)	101 (87.8)	173 (84.8	31 (86.1)	488 (85.3)
	African American	3 (5.5)	8 (7.8)	7 (11.7)	7 (6.1)	19 (9.3	2 (5.6)	46 (8.0)
	Hispanic	0	7 (6.9)	3 (5.0)	4 (3.5)	10 (4.9	1 (2.8)	25 (4.4)
	Other	2 (3.6)	4 (3.9)	0	3 (2.6)	2 (1.0	2 (5.6)	13 (2.3)

Table 2.41. Baseline Substance Abuse Characteristics of Subjects in Studies Longer than 6 months[1]

		Vivitrex Suspension (mg)						
		ALK21-003-EXT				ALK21-006	ALK21-006	All
		PBO[2]/190	190/190	PBO/380	380/380	380	Oral 50mg	Subjects
N Dosed		55	102	60	115	204	36	572
Dependence, N(%)	Alcohol only	55 (100)	102 (100)	60 (100)	115 (100)	146 (71.6)	23 (63.9)	501 (87.6)
	Opiate only/mixed	0	0	0	0	58 (28.4)	13 (36.1)	71 (12.4)
Lead-in Drinking[3], N(%)	Yes	50 (90.9)	96 (94.1)	53 (88.3)	102 (88.7)	115 (61.8)	21 (67.7)	437 (79.6)
	No	5 (9.1)	6 (5.9)	7 (11.7)	13 (11.3)	71 (38.2)	10 (32.3)	112 (20.4)

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10.11 Data tables from 120-day Safety Update Report (SUR)

10.11.1 Dropouts due to AEs

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
No. of subjects active after 8/31/2004	290	10	35	17	35	163	30	16
No. of subjects with an AE treatment/discontinuation	10 (3)	0	2 (6)	1 (6)	1 (3)	5 (3)	0	1 (6)
PSYCHIATRIC DISORDERS	3 (1)	0	1 (3)	0	1 (3)	1 (<1)	0	0
Completed suicide	1 (<1)	0	1 (3)	0	0	0	0	0
Depression	1 (<1)	0	0	0	1 (3)	0	0	0
Suicide attempt	1 (<1)	0	0	0	0	1 (<1)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (<1)	0	1 (3)	0	0	1 (<1)	0	0
Breast cancer *NOS*	1 (<1)	0	0	0	0	1 (<1)	0	0
Prostate cancer NOS	1 (<1)	0	1 (3)	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	2 (<1)	0	0	0	0	1 (<1)	0	1 (6)
Headache NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
Mental impairment NOS	1 (<1)	0	0	0	0	0	0	1 (6)
GASTROINTESTINAL DISORDERS	1 (<1)	0	0	0	0	0	0	1 (6)
Nausea	1 (<1)	0	0	0	0	0	0	1 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (<1)	0	0	1 (6)	0	0	0	0
Injection site induration	1 (<1)	0	0	1 (6)	0	0	0	0
Injection site mass	1 (<1)	0	0	1 (6)	0	0	0	0
Injection site reaction NOS	1 (<1)	0	0	1 (6)	0	0	0	0
INVESTIGATIONS	1 (<1)	0	0	0	0	1 (<1)	0	0
Liver function tests NOS abnormal	1 (<1)	0	0	0	0	1 (<1)	0	0

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Dropouts due to AEs (continued)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (<1)	0	0	0	0	1 (<1)	0	0
Rash generalised	1 (<1)	0	0	0	0	1 (<1)	0	0

[1] Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.
[2] Events with onset prior to first Vivitrex dose of ALK21-006Ext (if enrolled).
[3] Events with onset after first Vivitrex dose of ALK21-006Ext.
Note: Percentages are out of number of subjects active after 8/31/2004.

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10.11.2 N (%) subjects who experienced SAEs

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
No. of subjects active after 8/31/2004	290	10	35	17	35	163	30	16
No. of subjects with a SAE	25 (9)	0	3 (9)	1 (6)	1 (3)	16 (10)	3 (10)	1 (6)
PSYCHIATRIC DISORDERS	11 (4)	0	1 (3)	1 (6)	0	6 (4)	3 (10)	0
Alcoholism	4 (1)	0	0	1 (6)	0	1 (<1)	2 (7)	0
Suicide attempt	2 (<1)	0	0	0	0	2 (1)	0	0
Completed suicide	1 (<1)	0	1 (3)	0	0	0	0	0
Depression	1 (<1)	0	0	0	0	1 (<1)	0	0
Drug dependence	1 (<1)	0	0	0	0	0	1 (3)	0
Mood disorder NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
Suicidal ideation	1 (<1)	0	0	0	0	1 (<1)	0	0
INFECTIONS AND INFESTATIONS	3 (1)	0	1 (3)	0	0	2 (1)	0	0
Cellulitis	1 (<1)	0	1 (3)	0	0	0	0	0
Gastroenteritis NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
Pneumonia NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
VASCULAR DISORDERS	3 (1)	0	2 (6)	0	0	1 (<1)	0	0
Deep venous thrombosis NOS	2 (<1)	0	2 (6)	0	0	0	0	0
Hypertension NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
GASTROINTESTINAL DISORDERS	2 (<1)	0	0	0	0	1 (<1)	0	1 (6)
Gastric ulcer haemorrhage	1 (<1)	0	0	0	0	0	0	1 (6)
Ileus paralytic	1 (<1)	0	0	0	0	1 (<1)	0	0
SURGICAL AND MEDICAL PROCEDURES	2 (<1)	0	0	0	0	2 (1)	0	0
Coronary arterial stent insertion	1 (<1)	0	0	0	0	1 (<1)	0	0
Drug detoxification	1 (<1)	0	0	0	0	1 (<1)	0	0

(table continues on next page)

N (%) subjects who experienced SAEs (continued)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
CARDIAC DISORDERS	1 (<1)	0	0	0	0	1 (<1)	0	0
Angina unstable	1 (<1)	0	0	0	0	1 (<1)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (<1)	0	0	0	0	1 (<1)	0	0
Chest pain	1 (<1)	0	0	0	0	1 (<1)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<1)	0	0	0	0	1 (<1)	0	0
Laceration	1 (<1)	0	0	0	0	1 (<1)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (<1)	0	0	0	0	1 (<1)	0	0
Bunion	1 (<1)	0	0	0	0	1 (<1)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1)	0	0	0	0	1 (<1)	0	0
Breast cancer NOS	1 (<1)	0	0	0	0	1 (<1)	0	0
NERVOUS SYSTEM DISORDERS	1 (<1)	0	0	0	1 (3)	0	0	0
Cerebral arterial aneurysm	1 (<1)	0	0	0	1 (3)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (<1)	0	0	0	0	1 (<1)	0	0
Dyspnoea NOS	1 (<1)	0	0	0	0	1 (<1)	0	0

[1] Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.
[2] Events with onset prior to first Vivitrex dose of ALK21-006Ext (if enrolled).
[3] Events with onset after first Vivitrex dose of ALK21-006Ext.
Note: Percentages are out of number of subjects active after 8/31/2004.

10.11.3 N (%) of subjects with an injection site reaction

Injection Site Reactions	All Subjects	Placebo to 190mg ALK21-003EXT ALK21-010	190mg to 190mg ALK21-003EXT ALK21-010	Placebo to 380mg ALK21-003EXT ALK21-010	380mg to 380mg ALK21-003EXT ALK21-010	380mg ALK21006	Oral to 380mg ALK21-006Ext
Number of subjects active after 8/31/2004	276	10	35	17	35	163	16
No. (%) of subjects with Injection Site Reactions[1]							
Any ISR	63(23)	3(30)	11(31)	5(29)	10(29)	29(18)	5(31)
Injection Site Induration	38(14)	3(30)	8(23)	4(24)	6(17)	14(9)	3(19)
Injection Site Tenderness	24(9)		2(6)	2(12)	3(9)	14(9)	3(19)
Injection Site Pain	8(3)		2(6)	2(12)	3(9)	1(1)	
Injection Site Pruritus	7(3)		1(3)		1(3)	5(3)	
Injection Site Ecchymosis	2(1)					2(1)	
Other	4(1)					3(2)	1(6)

[1]Percentages are out of number of subjects active after 8/31/2004.

10.11.4 Most frequently reported AEs (by ≥ 5% of subjects in any treatment group)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
No. of subjects active after 8/31/2004	290	10	35	17	35	163	30	16
No. of subjects with an AE	207 (71)	8 (80)	28 (80)	12 (71)	24 (69)	115 (71)	17 (57)	10 (63)
INFECTIONS AND INFESTATIONS	92 (32)	5 (50)	11 (31)	5 (29)	11 (31)	49 (30)	7 (23)	6 (38)
Upper respiratory tract infection NOS	31 (11)	4 (40)	4 (11)	3 (18)	5 (14)	13 (8)	1 (3)	1 (6)
Nasopharyngitis	22 (8)	1 (10)	2 (6)	0	2 (6)	14 (9)	1 (3)	2 (13)
Sinusitis NOS	10 (3)	1 (10)	0	0	1 (3)	7 (4)	1 (3)	1 (6)
Influenza	6 (2)	0	1 (3)	0	2 (6)	1 (<1)	1 (3)	1 (6)
Urinary tract infection NOS	6 (2)	0	0	0	0	4 (2)	2 (7)	0
Gastroenteritis viral NOS	5 (2)	0	0	1 (6)	0	4 (2)	0	0
Herpes simplex	2 (<1)	0	1 (3)	0	0	0	0	1 (6)
Pneumonia NOS	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
Respiratory tract infection NOS	2 (<1)	0	0	0	0	0	1 (3)	1 (6)
Tooth infection	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	47 (16)	2 (20)	4 (11)	3 (18)	7 (20)	25 (15)	5 (17)	1 (6)
Arthralgia	17 (6)	2 (20)	2 (6)	2 (12)	3 (9)	5 (3)	2 (7)	1 (6)
Back pain	11 (4)	0	0	0	1 (3)	6 (4)	4 (13)	0
Pain in limb	5 (2)	0	0	1 (6)	1 (3)	3 (2)	0	0
Neck pain	4 (1)	0	0	1 (6)	1 (3)	2 (1)	0	0
Musculoskeletal chest pain	1 (<1)	0	0	1 (6)	0	0	0	0
PSYCHIATRIC DISORDERS	47 (16)	0	11 (31)	1 (6)	6 (17)	25 (15)	4 (13)	0
Depression	16 (6)	0	3 (9)	0	3 (9)	9 (6)	1 (3)	0
Anxiety NEC	11 (4)	0	1 (3)	1 (6)	0	8 (5)	1 (3)	0
Insomnia	11 (4)	0	4 (11)	1 (6)	1 (3)	5 (3)	0	0
Alcoholism	4 (1)	0	0	1 (6)	0	1 (<1)	2 (7)	0
Drug dependence	2 (<1)	0	0	0	0	0	2 (7)	0

(table continues on next page)

Most frequently reported AEs (by ≥ 5% of subjects in any treatment group) (continued)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
GASTROINTESTINAL DISORDERS	40 (14)	1 (10)	5 (14)	2 (12)	4 (11)	20 (12)	4 (13)	4 (25)
Nausea	9 (3)	0	1 (3)	0	0	6 (4)	0	2 (13)
Toothache	8 (3)	0	1 (3)	1 (6)	1 (3)	5 (3)	0	0
Diarrhoea NOS	5 (2)	0	1 (3)	0	0	1 (<1)	3 (10)	0
Dental discomfort	3 (1)	1 (10)	1 (3)	0	0	1 (<1)	0	0
Constipation	2 (<1)	0	0	0	2 (6)	0	0	0
Eructation	1 (<1)	0	0	0	0	0	0	1 (6)
Gastric ulcer haemorrhage	1 (<1)	0	0	0	0	0	0	1 (6)
Gastritis alcoholic	1 (<1)	0	0	0	0	0	0	1 (6)
Reflux oesophagitis	1 (<1)	0	0	1 (6)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	31 (11)	1 (10)	6 (17)	3 (18)	1 (3)	18 (11)	2 (7)	0
Fatigue	10 (3)	1 (10)	1 (3)	1 (6)	1 (3)	6 (4)	0	0
Influenza like illness	4 (1)	0	3 (9)	0	0	1 (<1)	0	0
Injection site induration	3 (1)	0	0	1 (6)	0	2 (1)	0	0
Fall	1 (<1)	0	0	1 (6)	0	0	0	0
Injection site mass	1 (<1)	0	0	1 (6)	0	0	0	0
Injection site reaction NOS	1 (<1)	0	0	1 (6)	0	0	0	0
NERVOUS SYSTEM DISORDERS	31 (11)	0	3 (9)	1 (6)	4 (11)	19 (12)	2 (7)	2 (13)
Headache NOS	13 (4)	0	1 (3)	0	1 (3)	10 (6)	1 (3)	0
Dizziness	4 (1)	0	0	0	2 (6)	1 (<1)	0	1 (6)
Sciatica	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
Mental impairment NOS	1 (<1)	0	0	0	0	0	0	1 (6)
INVESTIGATIONS	30 (10)	2 (20)	5 (14)	1 (6)	0	19 (12)	3 (10)	0
Blood bilirubin increased	2 (<1)	0	1 (3)	1 (6)	0	0	0	0
Cardiac murmur NOS	2 (<1)	1 (10)	1 (3)	0	0	0	0	0
Weight increased	1 (<1)	1 (10)	0	0	0	0	0	0

(table continues on next page)

Most frequently reported AEs (by ≥ 5% of subjects in any treatment group) (continued)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	27 (9)	2 (20)	1 (3)	2 (12)	6 (17)	11 (7)	5 (17)	1 (6)
Laceration	7 (2)	0	0	0	0	4 (2)	3 (10)	0
Limb injury NOS	4 (1)	0	0	1 (6)	2 (6)	1 (<1)	0	0
Animal bite	3 (1)	1 (10)	0	0	0	1 (<1)	0	1 (6)
Abrasion NOS	2 (<1)	0	0	0	2 (6)	0	0	0
Neck injury NOS	2 (<1)	1 (10)	0	0	0	1 (<1)	0	0
Joint dislocation NEC	1 (<1)	0	0	1 (6)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	24 (8)	1 (10)	2 (6)	1 (6)	1 (3)	16 (10)	3 (10)	0
Cough	8 (3)	0	0	1 (6)	0	7 (4)	0	0
Pharyngolaryngeal pain	5 (2)	0	2 (6)	0	0	3 (2)	0	0
Pulmonary congestion	1 (<1)	1 (10)	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	21 (7)	1 (10)	3 (9)	2 (12)	4 (11)	11 (7)	0	0
Rash NOS	7 (2)	1 (10)	0	0	2 (6)	4 (2)	0	0
Eczema NOS	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
Ecchymosis	1 (<1)	0	0	1 (6)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	15 (5)	1 (10)	0	3 (18)	1 (3)	9 (6)	1 (3)	0
Hypercholesterolaemia	6 (2)	0	0	1 (6)	1 (3)	4 (2)	0	0
Appetite decreased NOS	3 (1)	1 (10)	0	1 (6)	0	1 (<1)	0	0
Hyperglycaemia NOS	3 (1)	0	0	1 (6)	0	1 (<1)	1 (3)	0
VASCULAR DISORDERS	10 (3)	1 (10)	2 (6)	1 (6)	0	6 (4)	0	0
Hypertension NOS	7 (2)	1 (10)	1 (3)	0	0	5 (3)	0	0
Deep venous thrombosis NOS	2 (<1)	0	2 (6)	0	0	0	0	0
Hot flushes NOS	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	9 (3)	0	1 (3)	0	0	6 (4)	1 (3)	1 (6)
Menstruation irregular	2 (<1)	0	0	0	0	1 (<1)	0	1 (6)

(table continues on next page)

Most frequently reported AEs (by ≥ 5% of subjects in any treatment group) (continued)

System Organ Class (MedDRA) Preferred Term (MedDRA)	All Subjects[1]	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 190mg	Vivitrex ALK21-003Ext and ALK21-010 190mg to 190mg	Vivitrex ALK21-003Ext and ALK21-010 Placebo to 380mg	Vivitrex ALK21-003Ext and ALK21-010 380mg to 380mg	Vivitrex 380mg ALK21-006 and ALK21-006Ext	Oral Naltrexone[2] ALK21-006	Vivitrex Oral to 380mg[3] ALK21-006 Ext
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (2)	0	4 (11)	1 (6)	0	2 (1)	0	0
Basal cell carcinoma	1 (<1)	0	0	1 (6)	0	0	0	0
RENAL AND URINARY DISORDERS	5 (2)	0	1 (3)	0	0	2 (1)	2 (7)	0
CARDIAC DISORDERS	4 (1)	0	0	1 (6)	0	2 (1)	1 (3)	0
Bradycardia NOS	1 (<1)	0	0	1 (6)	0	0	0	0
IMMUNE SYSTEM DISORDERS	3 (1)	0	0	0	2 (6)	1 (<1)	0	0
EYE DISORDERS	2 (<1)	0	0	1 (6)	0	1 (<1)	0	0
Cataract NOS	1 (<1)	0	0	1 (6)	0	0	0	0

[1] Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.
[2] Events with onset prior to first Vivitrex dose of ALK21-006Ext (if enrolled).
[3] Events with onset after first Vivitrex dose of ALK21-006Ext.
Note: Percentages are out of number of subjects active after 8/31/2004.

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

/s/

Mwango Kashoki
12/8/2005 06:34:15 PM
MEDICAL OFFICER

Celia Winchell
12/19/2005 01:23:20 PM
MEDICAL OFFICER
I concur with Dr. Kashoki's conclusions. Please see my supervisory memo.

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	10/24/05
To:	Lisa Basham-Cruz, M.S., CSO Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170
From:	Charles E. Lee, M.D., Medical Officer Division of Pulmonary and Allergy Products, HFD-570
Through:	Lydia Gilbert-McClain, M.D., Medical Team Leader Division of Pulmonary and Allergy Products, HFD-570
Through:	Badrul A. Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products, HFD-570
Subject:	Medical Officer Consultation regarding adverse reactions with Medisorb Naltrexone, NDA 21-897

General Information

NDA/IND#:	NDA 21-897
Sponsor:	Alkermes, Inc.
Drug Product:	Medisorb Naltrexone
Request From:	Lisa Basham-Cruz, M.S., CSO Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170
Date of Request:	8/25/05
Date Received:	8/25/05
Materials Reviewed:	Consultation request NDA 21-897, N-000, 3/31/05 NDA 21-897, N-000, 8/8/05 NDA 21-897, N-000, 9/6/05 Patient records and pathology report for patients with eosinophilic pneumonia References

1. EXECUTIVE SUMMARY

A severe injection site reaction, eosinophilia and pneumonias with eosinophilia, and urticaria and angioedema were noted in the drug development program for Medisorb Naltrexone, a depot formulation of naltrexone being developed by Alkermes, Inc. for the treatment of alcohol dependence. DAARP has asked for DPAP's opinion if these reactions are consistent with an allergic/immunologic response to treatment, if the reactions be predicted or prevented, and what treatments are recommended for patients experiencing similar reactions.

It is unclear if these reactions have an immunologic etiology.

The severe injection site reaction may be consistent with an immunologic, a non-immunologic or toxic response, or could involve multiple types of immune responses. The localized nature of the reaction, the indolent course, and the absence of urticaria, angioedema, wheezing, or other symptoms of immediate hypersensitivity make it unlikely that immediate hypersensitivity (IgE-mediated or Gell and Coombs Type I hypersensitivity) was involved in this reaction. In the absence of evidence for a specific immunologic etiology, it is not possible to determine if in vitro or in vivo testing could predict such a response. There is insufficient evidence to determine if similar reactions could be predicted or prevented. DPAP is reluctant to recommend a treatment for patients experiencing similar reactions because the mechanism for these reactions is unclear.

Eosinophilia may be associated with IgE-mediated conditions, such as asthma with allergic triggers, but its presence is not diagnostic for an allergic process. It is also unclear if the mechanism for the eosinophilia and the eosinophilic pneumonias noted in the drug development program are the same. It is unclear if an immunologic process is involved. In the absence of evidence for a specific immunologic etiology, it is not possible to determine if in vitro or in vivo testing could predict the development of eosinophilia or eosinophilic pneumonia and impossible to determine if similar reactions could be prevented. Long-term follow-up in study ALK21-003-EXT suggested that patients with eosinophilia had normalization of their eosinophil counts by Week 40. No treatment may be necessary for patients that develop eosinophilia with Medisorb Naltrexone treatment. If eosinophilia is noted in patients being treated with the drug, it would be reasonable to follow eosinophil counts until they normalize. Patients developing eosinophilic pneumonia should have the drug discontinued. As with the two patients who developed eosinophilic pneumonias, treatment with systemic corticosteroids may be indicated once infection has been excluded.

Data suggest that urticaria and angioedema are associated with Medisorb Naltrexone. None of the adverse events for urticaria or angioedema met the criteria for a serious adverse event and none were associated with symptoms of anaphylaxis, such as wheezing, laryngeal edema, hypotension, or syncope. All of the adverse events involved only the skin. Only one of the patients required systemic corticosteroids. None required epinephrine, other parenteral medications, or intravenous fluids. The absence of more serious reactions in the drug development program, such as anaphylaxis, does not exclude the possibility that they may be noted when larger numbers of patients are exposed, however.

Although it is not possible to rule out an IgE-mediated mechanism for these reactions, it is more likely that they are a result of non-IgE-mediated mast cell degranulation, as may be seen with iodinated radiocontrast media. IgE-mediated hypersensitivity is an immune mechanism, and sensitization is required before symptoms may occur from subsequent exposure. Two of the reactions occurred with the first dose, and one occurred just two days after drug administration, an insufficient period of time for the development of an immune response. Many of the patients had subsequent doses of drug without a recurrence of symptoms, which would be unusual for an IgE-mediated process. Appropriate treatment of urticaria or angioedema without associated respiratory or cardiovascular symptoms includes discontinuation of treatment and H1-receptor antagonists. If extensive or severe cutaneous involvement is present, H2-receptor antagonists and/or systemic corticosteroids may be used adjunctively.

Although it is more likely that urticaria and angioedema noted in the drug development program do not have an immune etiology, it is reasonable for the applicant to determine if the product elicits an immune response in humans. If positive in vivo or in vitro tests of drug specific antibody are found, it may be possible to assess if they may be predictive of these reactions. There may be some benefit in determining if naltrexone-specific, carboxymethylcellulose (CMC)-specific, or naltrexone/CMC-specific antibody is present in patients with these reactions. Percutaneous skin testing or in vitro tests drug-specific IgE may of benefit in determining if there is an IgE-mediated process. In vitro tests of drug-specific IgM, or IgG may be helpful in determining if a Type III or immune complex-mediated reaction is present. Delayed hypersensitivity skin testing or patch testing may be of benefit in determining if a Type IV or delayed hypersensitivity reaction is involved.

2. BACKGROUND

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) has asked the Division of Pulmonary and Allergy Products (DPAP) to consult on a severe injection site reaction, eosinophilia and pneumonias with eosinophilia, and urticaria and angioedema noted in the drug development program for Medisorb Naltrexone.

Medisorb Naltrexone is a depot formulation of naltrexone being developed for the treatment of alcohol dependence. The applicant is Alkermes, Inc. Naltrexone, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone is also related to the opioid antagonist, naloxone [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

Naltrexone reversibly blocks the effects of opioids by competitive binding at opioid receptors. The drug is a μ-opioid antagonist. The applicant states that the drug has few, if any intrinsic actions besides its opioid blocking properties and papillary constriction [Module 2, Section 2.2.1, introduction.pdf, pages 1-2; Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

When co-administered with morphine, on a chronic basis, naltrexone blocks the physical dependence to morphine, heroin and other opioids. The administration of naltrexone is not associated with the development of tolerance or dependence. In subjects physically dependent on

opioids, naltrexone will precipitate withdrawal symptomatology [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. It has been proposed that, in patients with alcohol dependence, blockade of the endogenous opioid peptides leads to decreased craving for alcohol, decreased urge to drink, and reduction in the consumption of alcohol [Module 2, Section 2.2.1, introduction.pdf, pages 1-2].

Medisorb Naltrexone (naltrexone long-acting injection) is a combination of extended-release microspheres of naltrexone incorporated into a biodegradable matrix of polyactide-co-glycolide (PLG). The microspheres are combined with a diluent and the combination is injected intramuscularly. Excipients in the diluent are [redacted] carboxymethylcellulose sodium [redacted] polysorbate 20 [redacted] sodium chloride [redacted], and water for injection [Module 2, Section 2.3.P, drug-product.pdf, page 5].

Medisorb Naltrexone (naltrexone long-acting injection) is supplied in single use kits. Each kit contains one 380 mg vial of Medisorb Naltrexone microspheres, containing 4.0 mL (to deliver 3.4 mL) Diluent for the suspension Medisorb Naltrexone, one 5 mL syringe, one ½" 20 gauge needle, and gauge needles with safety device [Module 1, Section 1.1, draft-labeling.pdf, pages 10-11, 32-33, 38].

The proposed indication for Medisorb Naltrexone is the treatment of alcohol dependence. Proposed labeling states that [redacted] [Module 1, Section 1.1, draft-labeling.pdf, pages 10-11].

The recommended dose of Medisorb Naltrexone is 380 mg IM every 4 weeks or once a month over an indefinite period of time. There were 572 subjects enrolled in extension trials in the drug development program who continued on treatment for more than 6 months [Module 1, Section 1.1, draft-labeling.pdf, pages 32-33].

DAARP has asked DPAP to review and comment on (1) injection site reactions, (2) eosinophilia and pneumonias with eosinophilia, and (3) urticaria and angioedema noted in the drug development program for Medisorb Naltrexone. In addition, DAARP has asked for DPAP's opinion if these reactions are consistent with an allergic/immunologic response to treatment, if the reactions be predicted or prevented, and what treatments are recommended for patients experiencing similar reactions. These adverse events are discussed below.

3. ADVERSE EVENTS ASSOCIATED WITH ORAL NALTREXONE

An oral formulation of naltrexone is currently marketed in the United States. While extensive clinical studies evaluating the use of the oral form of naltrexone HCl in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of naltrexone HCl use, placebo-controlled studies employing up to 5-fold higher doses of naltrexone HCl (up to 300 mg/day) than that recommended for use in opiate receptor blockade have shown that naltrexone HCl causes hepatocellular injury in a substantial proportion of patients exposed at

higher doses [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

Naltrexone HCl has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7-10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone HCl, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%). Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

During the naltrexone HCl clinical trials in opioid addiction, difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache were reported at an incidence rate of more than 10%. The incidence was less than 10% for loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency and chills [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

Adverse events that have been reported from postmarketing use of naltrexone HCl include anorexia, asthenia, chest pain, fatigue, headache, hot flushes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnea, rash, increased sweating, and vision abnormalities [Mosby's Drug Consult, 15th Edition, 2005, in STAT!Ref OnLine].

DPAP comments:
Eosinophilia, eosinophilic pneumonia, urticaria, and angioedema have not been associated with use of oral naltrexone [Module 2, Section 2.7.4, summary-clin-safety.pdf, pages 3-15; NDA 21-897, N-000, 8/8/05, Attachment I, page 2].

4. CLINICAL DRUG DEVELOPMENT PROGRAM

There were nine clinical studies in the drug development program for Medisorb Naltrexone. Of these nine clinical studies, seven were primary clinical studies and two were extension studies of a pivotal efficacy and safety study. There were five phase 1 and phase 2 clinical pharmacology and/or pharmacodynamics studies in the drug development program. There were two phase 3 studies in the drug development program, which included one pivotal phase 3 efficacy and safety study (ALK21-003) and one long-term safety study (ALK21-006). There were two ongoing extension studies of the pivotal phase 3 efficacy and safety study at the time of the NDA submission [Module 2, Section 2.5.5, clinical-overview.pdf, pages 50-51].

A total of 1232 subjects were enrolled in the nine clinical trials in the drug development program at the time of the NDA submission. There were 1049 subjects who had received Medisorb Naltrexone at the time of the NDA submission, with monthly administration for a period of up to 30 months. Total person-years exposure to Medisorb Naltrexone suspension or placebo in the studies of dependent subjects is summarized in Table 1 [Module 2, Section 2.5.5, clinical-overview.pdf, page 52]:

Table 1. Exposure to study treatment in Medisorb Naltrexone drug development program [Module 2, Section 2.5.5, clinical-overview.pdf, page 52].

Study treatment	Subjects, N	Subject-years of exposure
Placebo	214	79
Medisorb Naltrexone suspension,190 mg	265	203
Medisorb Naltrexone suspension,380 or 400 mg	661	393

5. INJECTION SITE REACTIONS

The most commonly observed injection site reactions in the clinical development program were tenderness, induration, and pain. Clinically significant injection site reactions appeared to be dose-related. Injection site reactions noted in the clinical development program are summarized in Table 2 [Module 2, Section 2.7.4, summary-clin-safety.pdf, pages 277-278].

Table 2. Injection site reactions in Medisorb Naltrexone drug development program [Module 2, Section 2.7.4, summary-clin-safety.pdf, page 278].

	Placebo		Medisorb Naltrexone 90 mg		Medisorb Naltrexone 380/480 mg	
	n	(%)	n	(%)	n	(%)
Total number of injections	1025		2644		5130	
Injections followed by injection site reaction	181	(18)	381	(14)	864	(17)
Clinically significant injection site reactions	18	(1.8)	54	(2.0)	137	(2.7)
Discontinuations due to injection site reactions	1	(<1)	2	(<1)	17	(<1)
Serious adverse event related to injection site reaction	0	(0)	0	(0)	1	(<1)

There was one patient in the drug development program who experienced a severe adverse event for an injection site reaction. Patient 246-013 was a 35-year old female enrolled in long-term safety study ALK21-006 who received her first and only dose of 380 mg of Medisorb Naltrexone on October 10, 2003. She noted tenderness at the injection site on October 27, 2003. On November 1, 2002, the patient had a 5" x 5" area of redness and tenderness at the injection site at the right buttock. She was started on Keflex and Alleve by the Principal Investigator. She returned for evaluation on November 6, 2003, and was discontinued from the study because of the adverse event. At that visit, the patient had an elevated WBC of 15,700/mcL and neutrophil count of 11,600/mcL, and a normal eosinophil count of 300/mcL [Module 5, alk21-006-246-013.pdf, pages 50, 73-74; Module 5, tab-fig-list-alk21-006.pdf, page 1585]. She was started on Augmentin and referred to an infectious disease specialist. She did not see the infectious disease specialist, but saw her primary care physician and a surgeon. The surgeon cultured the injection site. The culture was reported to be negative [Module 5, alk21-006-246-013.pdf, pages 50, 73-74].

The patient chose to go to the —, and was admitted on — [Module 5, alk21-006-246-013.pdf, pages 50, 73-74]. At admission to the — on —

—, she had an elevated WBC of 19,700/mcL, an elevated neutrophil count of 12,400/mcL, and an elevated eosinophil count of 4,770/mcL. At the —, the patient had a CT scan of the abdomen and pelvis, which showed a 12 cm area of inflammatory stranding and edema at the site of the injection. A cutaneous punch biopsy was obtained and the results were consistent with a "hypersensitivity reaction." She had an incision and debridement performed on —, but required a wide local excision on — because the wound continued to have necrotic edges. Pathology revealed a 13 x 11 x 9 cm area of fat necrosis [Module 5, alk21-006-246-013.pdf, pages 50, 73-74]. An allergy consultation concluded that the inflammation was secondary in part to an allergic response the Medisorb Naltrexone injection [NDA 21-897, N-000, 9/6/05, Cover Letter.pdf, Appendix III, page 17]. On —, her WBC was elevated at 12,600/mcL, neutrophils were slightly elevated at 7,220/mcL, and her eosinophil count was elevated at 2,270/mcL [NDA 21-897, N-022, 9/6/05, Cover Letter.pdf, Appendix II, page 9]. Her remaining hospital stay was reported to be without complications, and she was discharged from the — on — [Module 5, alk21-006-246-013.pdf, pages 50, 73-74].

DPAP comments:
The patient's onset of tenderness at the injection site on the fifth day post-dose would be somewhat early for an immune response to the patient's initial exposure to the drug product. It is still possible that there was some immunologic component to this patient's injection site reaction. If so, it is unclear what type of immunologic response may have been involved. It is also unclear if the CMC excipient may have had some role in the reaction. The prolonged time course of the reaction is likely to have been influenced by the depot formulation of the drug product.

The presentation could be also consistent with a non-immunologic or toxic response or could involve multiple types of immune responses, including B-cell mediated responses, such as local formation of antibody/antigen complexes (Arthus reaction or Gell and Coombs Type III hypersensitivity) or T-cell mediated responses (delayed hypersensitivity or Gell and Coombs Type IV hypersensitivity). The localized nature of the reaction and the indolent course, and the absence of urticaria, angioedema, wheezing, or other symptoms of immediate hypersensitivity make it unlikely that immediate hypersensitivity (IgE-mediated or Gell and Coombs Type I hypersensitivity) was involved in this reaction. Drug hypersensitivity reactions are discussed in practice parameters developed by the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology and in a review by Gruchalla.[1,2]

Although eosinophilia may be associated with IgE-mediated conditions, such as asthma with allergic triggers, its presence is not diagnostic for an allergic process. Although it is possible that the patient's eosinophilia was associated with the injection site reaction, it should be noted that eosinophilia was also noted in patients who did not have injection site reactions, and may be coincidental and unrelated finding. The dermatopathology report for the punch biopsy is not available, and there is no description of the findings that led to the interpretation of "hypersensitivity reaction," a non-specific term. There is also no description of the findings of the surgical biopsy other than fat necrosis, which is not typical for an immunologic response. In summary, it is unclear if there is an immunologic component to this injection site reaction. If

there is an immunologic component, it is impossible to determine the immunologic mechanism of the reaction.

In the absence of evidence for a specific immunologic etiology, it is not possible to determine if in vitro or in vivo testing could predict such a response. There is insufficient evidence to determine if similar reactions could be predicted or prevented.

Percutaneous skin testing or in vitro tests of drug-specific IgE may of benefit in determining if there is an IgE-mediated process. In vitro tests of drug-specific IgM and IgG may be helpful in determining if a Type III or immune complex-mediated reaction is present. Delayed hypersensitivity skin testing or patch testing may be of benefit in determining if a Type IV or delayed hypersensitivity reactions is involved. In vivo and in vitro allergy testing is discussed in practice parameters developed by the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology.[3]

DPAP is reluctant to recommend a treatment for patients experiencing similar reactions because the mechanism for this reaction is unclear.

6. EOSINOPHILIA AND PNEUMONIAS WITH EOSINOPHILIA

Eosinophil counts were increased in study ALK21-003, the pivotal phase 3 efficacy and safety study, and study ALK21-006, the long-term safety study [Module 2, Section 2.7.4, summary-clin-safety.pdf, page 278].

At all visits in study ALK21-003, there was a dose-related increase in eosinophils in patients treated with Medisorb Naltrexone, compared with patients treated with placebo. These data are summarized in Table 3.

Table 3. Eosinophil counts, study ALK21-003 [Module 5, Study Report ALK21-003, Section 14.3.5, study-report-body-alk21-003l, pages 153-154].

	Placebo	Medisorb Naltrexone 190 mg	Medisorb Naltrexone 380 mg
Baseline			
N	209	209	205
Eosinophils/µL (SD)	171 (120)	173 (134)	181 (128)
Day 28, change from baseline			
N	195	191	192
Eosinophils/µL (SD)	21 (110)	65 (151)	91 (189)
Day 56, change from baseline			
N	172	172	164
Eosinophils/µL (SD)	20 (121)	48 (138)	58 (158)
Day 84, change from baseline			
N	161	159	153
Eosinophils/µL (SD)	15 (133)	65 (166)	85 (194)
Day 112, change from baseline			
N	140	142	138
Eosinophils/µL (SD)	9 (113)	53 (127)	54 (153)
Day 140, change from baseline			
N	131	136	130

	Placebo		Medisorb Naltrexone 190 mg		Medisorb Naltrexone 380 mg	
Baseline						
Eosinophils/μL (SD)	8	(114)	54	(187)	83	(183)
Day 168, change from baseline						
N	120		118		123	
Eosinophils/μL (SD)	11	(120)	61	(133)	90	(302)
Last visit post-baseline, change from baseline						
N	198		193		193	
Eosinophils/μL (SD)	12	(113)	48	(146)	103	(289)

ALK21-003-EXT was long-term follow-up extension study to ALK21-003. Patients who were randomized to placebo in ALK21-003 were switched to Medisorb Naltrexone 190 mg or 380 mg at 24 weeks. Patients switched from placebo to Medisorb Naltrexone 190 mg had a small increase in eosinophil count after 16 weeks, at Week 40. Patients switched from placebo to Medisorb Naltrexone 380 mg had an increase in eosinophil counts after 8 and 16 weeks, at Weeks 32 and 40, respectively. Eosinophil counts normalized in the Medisorb Naltrexone 380 mg group by Week 40. These data are summarized in Table 4.

Table 4. Eosinophil counts, study ALK21-003-EXT [Module 5, Study Report ALK21-003-EXT, Section 14.3, tab-fig-list-alk21-003ext, pages 454-455].

	Placebo to Medisorb Naltrexone 190 mg		Medisorb Naltrexone 190 mg		Placebo to Medisorb Naltrexone 380 mg		Medisorb Naltrexone 380 mg	
Week 24, change from baseline								
N	51		94		59		111	
Eosinophils/μL (SD)	0	(130)	60	(130)	20	(100)	90	(320)
Week 32, change from baseline								
N	46		86		49		91	
Eosinophils/μL (SD)	0	(140)	70	(150)	110	(280)	50	(220)
Week 40, change from baseline								
N	41		79		37		75	
Eosinophils/μL (SD)	40	(140)	50	(170)	70	(140)	10	(190)

In study ALK21-006, there was a dose-related increase in eosinophils in patients treated with Medisorb Naltrexone, compared with patients treated with oral naltrexone. These data are summarized in Table 5.

Table 5. Eosinophil counts, study ALK21-006 [Module 5, Study Report ALK21-006, Section 14.3, study-report-body-alk21-006.pdf, pages 74-75].

	Oral Naltrexone 50 mg		Medisorb Naltrexone 380 mg	
Baseline				
N	65		369	
Eosinophils/μL (SD)	170	(128)	186	(132)
Week 4, change from baseline				
N	62		334	
Eosinophils/μL (SD)	0	(136)	26	(191)
Week 8, change from baseline				
N	52		309	
Eosinophils/μL (SD)	-2	(106)	25	(148)
Week 12, change from baseline				
N	47		276	

	Oral Naltrexone 50 mg		Medisorb Naltrexone 380 mg	
Eosinophils/μL (SD)	-9	(113)	14	(136)
Week 16, change from baseline				
N	43		256	
Eosinophils/μL (SD)	-24	(109)	25	(197)
Week 20, change from baseline				
N	39		230	
Eosinophils/μL (SD)	-7	(128)	-7	(153)
Week 24, change from baseline				
N	36		207	
Eosinophils/μL (SD)	-30	(125)	-5	(143)

There were also two patients in study ALK21-003 who developed serious adverse events of pneumonia with eosinophilia. These serious adverse events are summarized below.

ALK21-003-211-021 — was a 61-year-old male with a previous history of alcohol dependence, periodontal disease, deep vein thrombosis, gastroesophageal reflux, prostatitis, hypercholesterolemia, sulfa allergy, arthritis, and attention deficit disorder. Concomitant medications included piroxicam, atorvastatin, amphetamine/dextroamphetamine, among others. He developed general malaise, myalgias, low-grade temperature, burning on urination, cough, and pleuritic chest pain over the three days following his second injection of Medisorb Naltrexone and was hospitalized and treated with levofloxacin for presumed pneumonia. He was discharged after three hospital days, but developed increasing dyspnea and was readmitted later the same day. His oxygen saturation was 87% on room air. A chest CT showed diffuse, patchy, ground-glass opacities. Peripheral white blood cell count was 11,200 with 15% eosinophils and BAL from bronchoscopy revealed a white blood cell count of 330 with 65% eosinophils. Treatment was begun with intravenous steroids. He improved and was discharged from hospital on oral steroids and oxygen at night on the eight hospital day. Eosinophilia and chest X-ray infiltrates cleared over the next two months. The investigator has assessed that this event was possibly related to the study drug. The patient did not receive any further injections of Medisorb Naltrexone [Module 5, Study Report ALK21-003, Section 14.3.2, study-report-body-alk21-003.pdf, pages 179-180].

ALK21-003-212-020 — was a 45-year-old male with a history of alcohol dependence, seasonal allergies, asthma, eczema, and possible borderline hypertension. Concomitant medications included fluticasone propionate/salmeterol inhaler and mometasone furoate nasal spray. He received 3 doses of Medisorb Naltrexone, 380 mg. Three days after receiving his third dose, he was seen in an urgent care center with a one week history of cough, malaise, and increasing shortness of breath. He reported that he was diagnosed with bilateral pulmonary infiltrates with hypoxemia, and was sent home on oral antibiotics. His symptoms continued to worsen, and on the next day he presented to a hospital emergency room. He was noted to have bilateral pulmonary infiltrates with alveolar and interstitial components as well as marked hypoxemia and was admitted to the intensive care unit. He was treated for both bacterial pneumonia and a possible allergic reaction with broad spectrum antibiotics, corticosteroids, bronchodilators, intravenous ranitidine, and diphenhydramine. Complete blood count revealed white blood cell count (WBC) 13.8, with 77% neutrophils, 8% monocytes, and 7.1% eosinophils. He rapidly improved with a combination of bronchodilators, antibiotics, and glucocorticoid

treatment. The day prior to discharge [redacted], the subject's oxygen saturation on room air oxygen was 93% and 92% post-exercise. The subject was discharged without oxygen on the fourth hospital day. Discharge medications included the following: (1) prednisone taper; (2) salmeterol/fluticasone; (3) cefuroxime; (4) azithromycin; (5) famotidine; and (6) albuterol. Prednisone therapy was continued for 2 months. Two months after admission, the subject was asymptomatic, physical examination was normal, but his eosinophil count remained elevated at 8.1%. The investigator initially determined that the interstitial pneumonia was probably not related to the study drug, but later changed his assessment to possibly related to study drug [Module 5, Study Report ALK21-003, Section 14.3.2, study-report-body-alk21-003.pdf, pages 180-181].

These two reports were submitted for independent expert review by [redacted] He concurred with the investigator's assessment that the first subject had eosinophilic pneumonia. He felt that the second subject more likely had a community acquired pneumonia [Module 2, Section 2.7.4, summary-clin-safety.pdf, page 282].

DPAP comments:
As noted earlier, eosinophilia may be associated with IgE-mediated conditions, such as asthma with allergic triggers, but its presence is not diagnostic for an allergic process. It is also unclear if the mechanism for the eosinophilia and the eosinophilic pneumonias is the same, and it is unclear if an immunologic process is involved. In the absence of evidence for a specific immunologic etiology, it is not possible to determine if in vitro or in vivo testing could predict the development of eosinophilia or eosinophilic pneumonia and impossible to determine if similar reactions could be prevented.

Long-term follow-up in study ALK21-003-EXT suggested that patients with eosinophilia had normalization of their eosinophil counts by Week 40. These data suggest that no treatment is necessary for patients that develop eosinophilia with Medisorb Naltrexone treatment. If eosinophilia is detected in these patients, it would be reasonable to follow eosinophil counts until they normalize.

Patients developing eosinophilic pneumonia should have the drug discontinued. As with the two patients who developed eosinophilic pneumonias, treatment with systemic corticosteroids may be indicated once infection has been excluded.

7. URTICARIA AND ANGIOEDEMA

Among 1090 patients exposed to Medisorb Naltrexone in controlled studies in the applicant's drug development program, there were 15 patients (1.4%, 15/1090) with 20 adverse events (1.8%, 20/1090) for urticaria and/or angioedema. There were no patients treated with placebo who had urticaria and/or angioedema [NDA 21-897, N-000, 8/9/05, cover-letter.pdf, pages 2-3].

Adverse events for urticaria and angioedema in these studies are summarized in Table 6. None of the adverse events for urticaria or angioedema met the criteria for serious adverse events. There were two patients who discontinued from the study because of these adverse events. Two of these events occurred after the first dose of Medisorb Naltrexone; the remainder occurred after

the second to the 19th dose of medication. Onset of symptoms occurred from one day to 32 days after the most recent dose. None of the events resulted in a hospitalization. Two of these adverse events were associated with concomitant use of a sulfa drug. Nine of the events did not require treatment; most of those events that required treatment were treated with H1-antihistamines. One patient required oral prednisone. No patient required treatment with epinephrine. Ten of the twenty patients with these events received from one to 20 subsequent doses of Medisorb Naltrexone without reaction [NDA 21-897, N-000, 8/9/05, cover-letter.pdf, pages 2-15].

DPAP comments:
The data suggest that urticaria and angioedema are associated with Medisorb Naltrexone. None of these reactions met the criteria for serious adverse events and none of the reactions was associated with symptoms of wheezing, laryngeal edema, hypotension, or syncope. All of the reactions involved only the skin. Only one of the patients required systemic corticosteroids. None required epinephrine, intravenous fluids, or other parenteral medications. The absence of more serious reactions in the drug development program, such as anaphylaxis, does not exclude the possibility that they may be noted when larger numbers of patients are exposed.

Although it is not possible to rule out an IgE-mediated mechanism for these reactions, it is more likely that they are a result of non-IgE-mediated mast cell degranulation, as may be seen with opiates such as morphine and codeine and with iodinated radiocontrast media. IgE-mediated hypersensitivity is an immune mechanism, and sensitization is required before symptoms result from subsequent exposure. Two of the reactions occurred with the first dose, one just two days after drug administration, an insufficient period of time for the development of an immune response. Many patients had subsequent doses of drug without a recurrence of symptoms, which would be unusual for an IgE-mediated process.

Although it is more likely that urticaria and angioedema noted in the drug development program do not have an immune etiology, it is reasonable for the applicant to determine if the product elicits an immune response in humans. If positive in vivo or in vitro tests of drug specific antibody are found, it may be possible to assess if they may be predictive of these reactions. There may be some benefit in determining if naltrexone-specific, carboxymethylcellulose (CMC)-specific, or naltrexone/CMC-specific antibody is present in patients with these reactions. Percutaneous skin testing or in vitro tests drug-specific IgE may of benefit in determining if there is an IgE-mediated process.[1, 3]

Appropriate treatment of urticaria or angioedema without associated respiratory or cardiovascular symptoms includes discontinuation of treatment and H1-receptor antagonists. If extensive or severe cutaneous involvement is present, H2-receptor antagonists and/or systemic corticosteroids may be used adjunctively.

Table 6. Summary of adverse events for urticaria and angiodema occurring in controlled trials for Medisorb Naltrexone [NDA 21-897, N-000, 8/9/05, cover-letter.pdf, pages 2-15].

Index number for adverse event	Study	Pt no.	Medisorb Naltrexone Dose	Reaction	Dose number	Days from most recent dose	Days from initial dose	Subsequent doses without reaction	Treatment	Comments
1	ALK21-002	224-016	400 mg	Angioedema	2	12 days	38 days	0	H1 and H2 antihistamines, topical corticosteroids	Discontinued because of this adverse event
2	ALK21-003	202-004	380 mg	Face edema	6	4 days	209 days	0	H1 antihistamine	
3	ALK21-003-EXT	209-015	380 mg	Urticaria	19	9 days	515 days	17	H1 antihistamine, topical corticosteroid, prednisone	
4, 5	ALK21-003-EXT	212-003	190 mg	Injection site urticaria	7	1 day	180 days	-----	No treatment required	
				Urticaria	7	7 days	187 days	0	No treatment required	Discontinued because of this adverse event
6, 7	ALK21-003	217-003	380 mg	Pruritic rash	2	4 days	32 days	-----	No treatment required	
				Urticaria	4	9 days	100 days	2	H1 antihistamine	
8	ALK21-003	217-029	190 mg	Urtiicaria	6	10 days	150 days	0	H1 antihistamine, topical corticosteroid	
9	ALK21-003	217-030	190 mg	Urticaria	3	12 days	74 days	3	H1 antihistamine	
10	ALK21-003	224-026	190 mg	Urticaria, face edema	6	7 days	146 days	0	No treatment required	
11	ALK21-003	225-016	190 mg	Face edema	1	2 days	2 days	4	No treatment required	
12	ALK21-003	227-006	190 mg	Urticaria	6	18 days	157 days	20	H1 antihistamine	Concomitant sulfa drug
13, 14	ALK21-006	214-011	380 mg	Urticaria	8	12 days	223 days	-----	H1 antihistamine	
				Urticaria	9	7 days	245 days	5	H1 antihistamine	
15	ALK21-006	237-010	380 mg	Urticaria	5	24 days	136 days	10	Topical tacrolimus	
16, 17	ALK21-006	245-014	380 mg	Urticaria	2	11 days	37 days	-----	No treatment required	Concomitant sulfa drug
				Face edema	6	32 days	194 days	1	No treatment required	
18	ALK21-006	250-013	380 mg	Urticaria	1	18 days	18 days	5	Pseudoephedrine	
19, 20	ALK21-006	250-023	380 mg	Face edema	3	4 days	62 days	-----	No treatment required	
				Face edema	5	2 days	116 days	1	No treatment required	

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2. Gruchalla RS. J Allergy Clin Immunol; 111(2):S548-S559, 2003.

3. Joint Task Force on Practice Parameters, AAAAI, ACAAI, JCAI. Ann Allergy Asthma Immunol; 75(6 Part 2):543-625, 1995.

cc: Division File, NDA 21-897, N-000, 3/31/05
HFD-170/Kashoki/Medical Reviewer
HFD-170/Winchell/Medical Team Leader
HFD-170/Basham-Cruz/Project Manager
HFD-570/Lee/Medical Reviewer
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Chowdhury/Division Director
HFD-570/Barnes/CPMS

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/s/

Charles Lee
10/31/2005 02:55:39 PM
MEDICAL OFFICER

Lydia McClain
10/31/2005 03:02:52 PM
MEDICAL OFFICER
I concur

Badrul Chowdhury
10/31/2005 04:08:37 PM
MEDICAL OFFICER