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.

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