### 7.1.3.3 Other significant adverse events

Due to the antagonist effects of naltrexone at the mu opioid receptor, there is a potential risk for dysphoria and other mood changes, as well as subsequent suicide in naltrexone-treated patients. In a placebo-controlled study in which patients with obesity were randomized to treatment with placebo or oral naltrexone 300 mg/day, 19% of patients in the oral naltrexone group developed non-serious elevations in serum transaminases after 3-8 weeks of treatment, compared to 0% of placebo-treated patients.

The Medisorb Naltrexone database suggested that, as a result of the route of administration, the drug may be associated with injection site reactions. Descriptions of the types of reactions were consistent with an inflammatory type response. The safety database also contained information regarding elevations in eosinophil count, a case of eosinophilic pneumonia, and reports of rash, urticaria, and angioedema. Together, the adverse events were suggestive of an allergic reaction following study treatment.

Therefore the safety database was assessed for evidence of increased risk of suicide, elevated LFTs, and allergic reactions in Medisorb Naltrexone patients. In addition, the specific type and severity of injection site reactions were evaluated.

#### *7.1.3.3.1 HEPATOTOXICITY*

Alkermes is of the opinion that the risk of hepatocellular injury from Medisorb Naltrexone is considerably lower than that of oral naltrexone because:

- Whereas the total monthly dose at which hepatotoxicity was observed with oral naltrexone (300 mg/day) would be 8400 mg, the total monthly dose of Medisorb Naltrexone is 380 mg (which is 22-fold lower than the total monthly dose of oral naltrexone).
- Administration of Medisorb Naltrexone suspension by gluteal IM injection avoids first-pass hepatic metabolism.
- Medisorb Naltrexone will be dispensed in single-dose kits and will be administered by a health care provider, reducing the risk of patient overdose.

Upon review of the safety data, Alkermes found that in alcohol-dependent subjects treated with Medisorb Naltrexone suspension the hepatic safety profile was indistinguishable from that of placebo, with assessments of ALT, AST, GGT, and total bilirubin. Also, single-dose IM administration of relatively high doses (141, 269, 530 and 784 mg) of Medisorb Naltrexone to healthy subjects did not result in hepatotoxicity.

Using the datasets *iss-ae_3.xpt* and *iss-labs.xpt* I calculated the number of patients who experienced a liver-related adverse event. I searched *iss-ae_3.xpt* for all terms consistent with hepatocellular injury, first by system organ class (gastrointestinal disorders, hepatobiliary disorders, and investigations), and then by specific terms including: AST, ALT, GGT, ALP,

SGPT, SGOT, LFT, liver, liver function, liver enzyme, laboratory test, aspartate, alanine, bilirubin, alk phos, glutamyltransferase, hepatitis, and jaundice.

I then searched the *iss-labs.xpt* dataset using the variable "LBNAME," under which were coded tests for AST (SGOT), ALT (SGPT), alanine transaminase, aspartate transaminase, total bilirubin, and total bilirubin (mg/dL). These categories were collapsed for ease of analysis. In addition, I used the variable "LBFLAG" to identify all patients with high values for any of the lab tests. This subset of patients was merged with the subset from the *iss-ae.xpt* dataset for comparison of events between active- and placebo-treated patients.

#### 7.1.3.3.1.1 Reviewer's Analysis: Patients with Hepatic-Related Adverse Events

7.1.3.3.1.1.1 Hepatic-related events – Studies of 4-6 month's exposure

Based on the *iss-ae_3.xpt* dataset, 4.8% of all patients (52/1090) in the 4-6 month trials experienced adverse events suggestive of hepatocellular injury. Most patients reported more than one type of hepatic-related injury. Only 1 of these AEs was considered serious (Subject ALK21003-230-024, 190-mg, cholelithiasis) but, based on my review of the patient narrative, was not related to study treatment.

The frequency of hepatic-related AEs in the combined Medisorb Naltrexone subset was 4.6% (37/811). This was lower than the frequency in the placebo group (5.6% (12/124)), and was comparable to the frequency in the oral naltrexone group (4.6% (3/65)). The risk of hepatic-related AEs did not appear to increase with increasing doses of Medisorb Naltrexone: 4.8% (10/210) of the 190-mg patients, 4.5% (26/576) of the 380-mg patients, and 4% (1/25) of the 400-mg patients.

Listed in Table 7.1.3.3.1.1 (below) are the types of events that were hepatic-related.

Liver function test (LFT) abnormalities/increases were the most commonly occurring. Of the 1090 patients with 4-6 months of drug exposure, 67 patients (6.1%) had an elevation of AST, ALT, GGT, bilirubin, or alkaline phosphatase. The most frequent type of LFT abnormality was an elevation in GGT, however more placebo patients than naltrexone patients reported this AE (3.7% of placebo patients vs. 1.6% of Medisorb Naltrexone and 0% of oral naltrexone patients). There was no evidence of a dose response of GGT elevation among the Medisorb Naltrexone groups. The greater proportion of placebo patients with high GGT levels compared to Medisorb Naltrexone patients likely reflects a higher frequency of drinking in the placebo population than in the Medisorb Naltrexone patients.

AST increases were the next most common LFT change, with slightly more patients in the oral naltrexone and combined Medisorb Naltrexone groups (~ 1.5% each) experiencing this AE than in the placebo group (0.9%). With respect to ALT, patients in the combined 380/400-mg Medisorb Naltrexone group and the oral naltrexone groups were more likely to report ALT increases (1.5% and 1.2%, respectively) than placebo patients (0.9%).

Five patients were reported as having hepatitis (1 case of alcoholic hepatitis, and 3 cases of hepatitis C, and 1 case of "hepatitis NOS.")[6]. Two cases occurred during ALK21-003, and the remaining three during ALK21-006. None of the cases was considered serious. I reviewed the patient narratives and CRFs to evaluate for a relationship to study treatment. The narratives showed that patients experienced elevated LFTs either in the context of increased drinking or hepatitis C diagnosis. These factors make it difficult to ascertain whether Medisorb Naltrexone is associated with hepatitis, or whether it increases the risk of hepatitis in patients with predisposing factors.

REVIEWER COMMENT:
Overall, therefore, the data from the trials of 4-6 months' duration suggest that treatment with Medisorb Naltrexone is associated with a slightly increased risk of AST and ALT compared to placebo, however this risk is similar to that associated with oral naltrexone therapy. Therefore, Medisorb Naltrexone does not appear to offer a safety advantage – with respect to hepatotoxicity – over oral naltrexone. The risk of hepatitis following treatment with Medisorb Naltrexone appears to be low.



6 Subject ALK21006-247-006: alcoholic hepatitis; Subject ALK21006-255-004: hepatitis NOS; Subjects ALK21003-216-005, ALK21003-216-012, and ALK21006-252-009: hepatitis C.

**Table 7.1.3.3.1.1.1 Reviewer's Analysis: AEs suggestive of hepatocellular injury – 4 – 6 month Studies**

| SOC | HLT | PT/AE | All subjects N = 1090 | | Medisorb Naltrexone | | | | | | | | | | Oral NTX N = 65 | | Placebo N = 214 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 190 mg N = 210 | | 380 mg N = 576 | | 400 mg N = 25 | | 380/400 mg N = 601 | | All N = 811 | | | | | |
| | | | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| *Any LFT abnormality* | | | *67* | *6.15* | *12* | *5.72* | *33* | *5.73* | *3* | *12* | *36* | *6.0* | *48* | *5.91* | *4* | *6.16* | *15* | *7* |
| Investigations | Liver function analyses | GGT increased | 21 | 1.93 | 4 | 1.90 | 8 | 1.39 | 1 | 4.00 | 9 | 1.5 | 13 | 1.60 | 0 | 0.00 | 8 | 3.74 |
| | | AST increased | 15 | 1.38 | 3 | 1.43 | 8 | 1.39 | 1 | 4.00 | 9 | 1.5 | 12 | 1.48 | 1 | 1.54 | 2 | 0.93 |
| | | ALT increased | 13 | 1.19 | 1 | 0.48 | 8 | 1.39 | 1 | 4.00 | 9 | 1.5 | 10 | 1.23 | 1 | 1.54 | 2 | 0.93 |
| | | Liver function tests NOS abnormal | 12 | 1.10 | 2 | 0.95 | 7 | 1.22 | 0 | 0.00 | 7 | 1.2 | 9 | 1.11 | 1 | 1.54 | 2 | 0.93 |
| | | Hyperbilirubinaemia/ Bilirubin increased | 4 | 0.37 | 1 | 0.48 | 1 | 0.17 | 0 | 0.0 | 1 | 0.2 | 2 | 0.24 | 1 | 1.54 | 1 | 0.47 |
| | Tissue enzyme analyses NEC | Alk phos NOS increased | 2 | 0.18 | 1 | 0.48 | 1 | 0.17 | 0 | 0.00 | 1 | 0.2 | 2 | 0.25 | 0 | 0.00 | 0 | 0.00 |
| | | | | | | | | | | | | | | | | | | |
| *Any hepatitis* | | | *5* | *0.46* | *1* | *0.48* | *4* | *0.69* | *0* | *0.0* | *4* | *0.7* | | | *0* | *0.0* | *0* | *0.0* |
| Hepatobiliary disorders | Hepatocellular damage and hepatitis NEC | Hepatitis alcoholic | 1 | 0.09 | 0 | 0.00 | 1 | 0.17 | 0 | 0.00 | 1 | 0.2 | 1 | 0.12 | 0 | 0.00 | 0 | 0.00 |
| Infections and infestations | Hepatic viral infections | Hepatitis C | 3 | 0.28 | 1 | 0.48 | 2 | 0.35 | 0 | 0.00 | 2 | 0.3 | 3 | 0.37 | 0 | 0.00 | 0 | 0.00 |
| | Liver and spleen infections | Hepatitis NOS | 1 | 0.09 | 0 | 0.00 | 1 | 0.17 | 0 | 0.00 | 1 | 0.2 | 1 | 0.12 | 0 | 0.00 | 0 | 0.00 |

**Table 7.1.3.3.1.1.1 Reviewer's Analysis: AEs suggestive of hepatocellular injury – 4 – 6 month Studies** (continued)

| SOC | HLT | PT/AE | All Subjects N = 1090 | | Medisorb Naltrexone 190 mg N = 210 | | 380 mg N = 576 | | 400 N = 25 | | 300/400 N = 601 | | All N = 811 | | Oral NTX N = 65 | | Placebo N = 214 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| *Hepatomegaly - total* | | | *3* | *0.27* | *0* | *0.0* | *1* | *0.17* | *1* | *4* | *2* | *0.3* | *2* | *0.25* | *0* | *0.0* | *1* | *0.47* |
| Hepatobiliary disorders | Hepatobiliary signs and symptoms | Hepatomegaly | 2 | 0.18 | 0 | 0.00 | 1 | 0.17 | 1 | 4.00 | 2 | 0.3 | 2 | 0.25 | 0 | 0.00 | 0 | 0.00 |
| Investigations | Physical examination procedures | Liver palpable subcostal | 1 | 0.09 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.0 | 0 | 0.00 | 0 | 0.00 | 1 | 0.47 |
| | | | | | | | | | | | | | | | | | | |
| *Hepatobiliary disorders* | *Cholecystitis and cholelithiasis* | *Cholelithiasis* | *1* | *0.09* | *1* | *0.48* | *0* | *0.00* | *0* | *0.00* | *0* | *0.0* | *1* | *0.12* | *0* | *0.00* | *0* | *0.00* |

7.1.3.3.1.1.2 Hepatic-related events – Studies of > 6-months's duration

The *iss_ae_3.xpt* dataset showed that, among the 572 patients included in this subset of studies, 44 patients (7.9%) reported 54 AEs suggestive of hepatocellular injury, 4 of which were labeled as "serious." I reviewed the patient narratives and considered only 1 of the "serious" cases to be suggestive of a relationship to Medisorb Naltrexone (subject ALK21003-210-004: acute hepatitis)[7]. This case has previously been discussed in Section 7.1.2.2.4 and the narrative is located in the Appendix.

The types and number of hepatic-related AEs in the "> 6-months' exposure" categories of studies are listed in the table below.

**Table 7.1.3.3.1.1.2: Reviewer's Analysis: Hepatic-related AEs – studies of > 6 months' duration**

| System Organ class | Adverse Event/Preferred Term | Medisorb Naltrexone | | | | Oral NTX | |
|---|---|---|---|---|---|---|---|
| | | 190- mg N = 157 | | 380-mg N = 175 | | 50 mg N = 36 | |
| | | N | % | N | % | N | % |
| Investigations | *LFT abnormalities - Total* | 9 | 5.74 | 11 | 6.28 | 2 | 5.56 |
| | ALT increased | 3 | 1.91 | 1 | 0.57 | 0 | 0.00 |
| | AST increased | 1 | 0.64 | 2 | 1.14 | 0 | 0.00 |
| | Blood alkaline phosphatase NOS increased | 0 | 0.00 | 1 | 0.57 | 0 | 0.00 |
| | Blood bilirubin increased | 3 | 1.91 | 1 | 0.57 | 1 | 2.78 |
| | GGT increased | 1 | 0.64 | 1 | 0.57 | 1 | 2.78 |
| | Laboratory test abnormal NOS | 0 | 0.00 | 1 | 0.57 | 0 | 0.00 |
| | LFTs NOS abnormal | 1 | 0.64 | 4 | 2.29 | 0 | 0.00 |
| | | | | | | | |
| Hepatobiliary disorders, Investigations | Hepatomegaly; Liver palpable subcostal | 2 | 1.28 | 1 | 0.57 | 0 | 0.0 |
| | | | | | | | |
| Gastrointestinal disorders | Abdominal pain NOS; abdominal pain upper | 10 | 6.37 | 10 | 5.72 | 1 | 2.78 |
| | | | | | | | |
| Hepatobiliary disorders | Cholecystitis acute NOS; Cholelithiasis | 2 | 1.28 | 0 | 0.0 | 0 | 0.0 |
| | | | | | | | |
| Hepatobiliary disorders | Hepatitis acute | 1 | 0.64 | 0 | 0.00 | 0 | 0.00 |

The table shows that LFT abnormalities were the most frequently reported AE in this category of studies that was suggestive of hepatocellular injury. Slightly more patients treated with Medisorb Naltrexone 380-mg (6.3%) reported LFT abnormalities than did patients in the 190-mg

7 The other 3 SAEs were not considered related to study treatment and were as follows: Subject ALK21003-230-018 – abdominal pain; Subject ALK21003-209-031 – cholecystitis, elevated LFTs; Subject ALK21003-224-015 – abdominal pain.

group (5.7%) and the oral naltrexone group (5.6%). Patients administered Medisorb Naltrexone were also more likely to report abdominal pain. The sole case of hepatitis that was likely to be treatment related occurred in a patient in the 190-mg arm.

REVIEWER COMMENT:
The information regarding hepatic-related AEs that is available from the open label studies is consistent with the information from the blinded/controlled trials: treatment with Medisorb Naltrexone, particularly the higher doses, is associated with a slightly increased risk of LFT abnormalities. Again, however, no safety advantage of Medisorb Naltrexone over oral naltrexone was demonstrated.

#### 7.1.3.3.1.2 Reviewer's Analysis: Changes in Liver Function Tests

#### 7.1.3.3.1.3 LFT changes – Studies of 4-6 month's duration

This category of trials includes Study ALK21-002 which, as has been previously noted, was a 4-month study in patients with alcohol dependence. The other two trials in the category (ALK21-003 and -006) comprise at least 6 months of data. Given the shorter exposure duration in Study -002, as well as the relatively few number of Medisorb Naltrexone-treated patients (n = 25), I excluded this study from the analysis of the change in LFT values from baseline to Week 24/Month 6.

Laboratory data were contained in the dataset *iss_lbhz.xpt*. Using this dataset, I calculated the mean LFT values at Baseline and Week 24 (Appendix Table 10.7.a). Increases in LFT values were of interest, as these would indicate possible hepatocellular injury.

Only the patients in the oral naltrexone group showed a small increase in the mean AST at Week 24. The mean AST value for the other treatment groups either remained relatively unchanged or was slightly decreased. None of the treatment groups showed a numerical increase in the mean ALT, GGT, or total bilirubin levels at Week 24.

I also evaluated whether there was a significant difference in the *within-group* mean LFT values from Baseline to Week 24, and if there was a difference between treatment groups (active vs. placebo) with respect to the mean LFT values at Week 24 (Appendix Table 10.8.b). The Medisorb Naltrexone 190-mg group showed statistically significant (i.e. p-value $< 0.05$) decreases in mean AST, ALT, and GGT levels from baseline to Week 24. Similarly, there was a statistically significant decrease from baseline for the Medisorb Naltrexone 380-mg and oral naltrexone groups with respect to the Week 24 GGT values. There were also statistically significant decreases in the 380-mg and placebo groups with respect to the baseline Week 24 bilirubin values. However, fairly wide confidence intervals were associated with these values, making the finding of a low p-value less relevant.

I evaluated the *between-group differences* (i.e. between active and placebo groups) in mean LFT values at Week 24 (Appendix Table 10.8.b). The 380-mg and oral naltrexone groups showed statistically significantly greater increases in the Week 24 mean GGT values compared to the

placebo group. Again, however, the confidence intervals for these differences were considerably wide. The 380-mg group's mean Week 24 bilirubin value was also slightly larger than the placebo group (mean difference = 0.07 mg/dL) and this finding was statistically significant. Otherwise, the Week 24 values of AST and ALT for either of the Medisorb Naltrexone groups, while greater numerically, were not statistically different from those of the placebo group.

REVIEWER COMMENT:
Although confidence intervals and p-values were calculated, it is important to note that the analyses do not take into account that the study was powered on the basis of the primary efficacy endpoint, and not the safety analyses, or that there is an issue of multiplicity.

Nevertheless, the data suggest that treatment with Medisorb Naltrexone only slightly increases mean LFT values by the end of treatment. The end-of-treatment mean LFT values are not much greater than those for the placebo group, suggesting no considerably increased risk of hepatocellular injury compared. Also, the mean LFT values suggest no difference in hepatic effect of Medisorb Naltrexone versus oral naltrexone.

Finally, I evaluated the Applicant's shift tables to determine whether more Medisorb Naltrexone patients had changes in LFT values from normal to abnormal, or from abnormal to even more abnormal (Appendix Tables 10.7.c to f). Higher proportions of patients in the Medisorb Naltrexone 380-mg group (14%) and the oral naltrexone group (10%) had a shift in ALT value from normal to the high limit of normal than did placebo patients (7%) or the 190-mg group (6%). Additionally, 3% of patients in the oral naltrexone group had a shift in AST from the high limit of normal to 3x the upper limit of normal, compared to 0% in the other groups. Otherwise, there no shifts from normal to abnormal in the active groups that were considerably different from the shifts observed in the placebo group.

REVIEWER COMMENT:
Overall, therefore, the laboratory data from the 4-6 month category studies show that treatment with naltrexone, whether oral or Medisorb naltrexone, can cause slight increases in transaminases, particularly ALT. However, the increases are not considerably greater than those observed with placebo treatment. Also, the effects of Medisorb Naltrexone therapy are no better or worse than the effects of oral naltrexone therapy.

#### 7.1.3.3.1.4 LFT changes – > 6 month studies

This category of studies comprised ALK21-006, ALK21-003-EXT, and ALK21-010. Since study ALK21-006 was ongoing at the time of data cutoff, the number of subjects overall and in any given group at the later time points becomes quite small. Therefore the composite data are subject to fluctuations due events in individual subjects.

At the data cutoff date, the maximum duration of exposure to Medisorb Naltrexone was 30 months: 1 patient in the 380-mg group, and 3 patients in the 190-mg group. However, Alkermes provided information on for the changes in LFTs for only 2 years of study treatment. For patients in ALK21-003EXT and -010, the 2 year period of observation includes the 6 months of exposure in ALK21-003.

Alkermes evaluated the mean LFT values over time (i.e. every 4 weeks), the mean changes in LFT values over time, and the proportions of patients who shifted from normal to abnormal (or abnormal to more abnormal) over time (Applicant's SCS, Appendix Tables 2.7.4.43 through 2.7.4.45, P. 271-375). For subjects in ALK21-006, baseline considered to be the last pre-dose test value. For subjects in ALK21-003EXT or ALK21-010, baseline was the initial dose in study ALK21-003.

With respect to ALT, the median values at 24 weeks were somewhat higher in subjects in ALK21-003EXT or ALK21-010 who has previously been treated with placebo than in subjects who had been given active drug (either Medisorb Naltrexone or oral naltrexone). Abnormal ALT values were noted among all groups over time, but there was no shift towards a higher proportion of abnormal values, either any value above upper limit of normal or over 3xULN, with time. Thus, there did not appear to be a trend towards increasing ALT abnormalities with continued Medisorb Naltrexone treatment.

At the end of the first 24 weeks of treatment, mean and median GGT values were lower among subjects in the Medisorb Naltrexone 380-mg and oral naltrexone groups, compared with those in the placebo and Medisorb Naltrexone 190-mg. As was observed with the ALT values, GGT abnormalities were noted among all groups and at all time points, but there was no increase in the proportion of abnormal values over time.

There were no considerable increases in AST or bilirubin for any of the treatment groups from baseline to Week 100.

> REVIEWER COMMENT: The data from the studies of > 6 months' exposure therefore suggest that prolonged treatment with Medisorb Naltrexone does not confer an increased risk of abnormalities in tests of liver function.

### 7.1.3.4 Suicide

Patients with a history of substance abuse, including alcohol abuse/dependence, are at risk for suicide, whether or not they also have a history of depression. In addition, as a mu opioid antagonist, naltrexone may cause dysphoria and other mood changes that put patients at risk for suicide. In previous studies in patients with alcohol and narcotic dependence, depression, suicidal ideation, and suicide attempts have been reported in those treated with oral naltrexone. Therefore, the NDA data were reviewed to evaluate whether treatment with Medisorb Naltrexone was associated with an increased risk of these events.

*7.1.3.4.1 APPLICANT'S EVALUATION OF SUICIDE-RELATED EVENTS*

To identify potential suicide cases, Alkermes reviewed all verbatim terms that suggestive of suicidal behavior, suicidal ideation, suicide attempt, or completed suicide. The Applicant then calculated the proportion of patients in each treatment group who experienced these events, for both the 4-6 month studies and the > 6 month studies.

Alkermes found that, among the 1090 subjects who participated in the Medisorb Naltrexone studies with 4 to 6 months of exposure, 16 subjects (1.5%) experienced a suicide-related AE. One subject committed suicide (the suicide occurred after completion of study participation). In addition, 2 subjects attempted suicide, 1 made a suicidal gesture, and 12 (1%) reported suicidal ideation.

In study ALK21-003, Alkermes counted 3 suicide-related events in the Medisorb Naltrexone group (1% of subjects), and none in the placebo 380-mg groups. In the first 6 months of study ALK21-006, of the 10 suicide-related events that occurred in the Medisorb Naltrexone 380 group (3% of that group), 7 occurred in subjects with alcohol dependence (3% of that group) and 3 events occurred in subjects with opiate/mixed dependence (3% of that group). Three subjects (5%; 2 with alcohol dependence and 1 with opiate/mixed dependence) who received oral naltrexone in study ALK21-006 had suicide-related AEs.

In studies longer than 6 months, as of the data cutoff date, Alkermes identified a total of 3 subjects who reported suicidal ideation: 2 participants in the extension studies to ALK21-003 (both at the 190 mg dose level), and 1 subject in ALK21-006 (380 mg group) with mixed opiate/alcohol dependence. There were no suicide attempts or completed suicides after 6 months of treatment.

Alkermes noted that most of the suicide-related events reported during the Medisorb Naltrexone clinical program occurred in the context of either depressive symptoms or further substance abuse (either alcohol or other drugs).

*7.1.3.4.2 REVIEWER'S EVALUATION OF SUICIDE-RELATED EVENTS*

**7.1.3.4.2.1 Suicide-Related Events – Studies of 4 to 6 months' exposure**

Using the *iss_ae_3.xpt* dataset, I attempted to identify all cases consistent with suicide (completed suicide, attempted suicide, or suicidal ideation). I selected for AEs grouped under the SOC terms "psychiatric disorders" and "injury, poisoning, and procedural complications." I then selected cases using the following HLGTs: injuries; injuries by physical agents; chemical injury, overdose and poisoning; psychiatric disorder NEC; psychiatric and behavioral symptoms NEC; and suicidal and self-injurious behaviors NEC. I narrowed the cases further by then selecting for LLTs that were consistent with suicide e.g. accidental ingestion; deliberate self-harm; injury; intentional overdose; and overdose. Patients with an AE of "depression" were excluded, unless they also had a suicide-related AE.

Based on this process, I identified 19 patients (19/1090, 1.7%) who had 20 events suggestive of suicide in the studies of 4-6 months' exposure, 8 of whom experienced serious suicide-related AEs (see Section 7.1.2.2.3.1).

As shown in Table 7.1.3.4.2.1, suicidal ideation was the most common suicide-related AE, followed by suicide attempt. The proportion of patients who reported suicidal ideation and suicide attempt was highest in the oral naltrexone group (3.1% and 1.5%, respectively). In comparison, 1.4% of patients in the Medisorb Naltrexone 380-mg group reported suicidal ideation, and 0.9% reported a suicide attempt. Slightly fewer patients (1.0%) in the 190-mg group experienced suicidal ideation, and none reported suicide attempts. There were no patients in the placebo group who had either suicidal ideation or attempt.

The patient narratives of the suicide-related events that I considered to possibly drug related are provided in the Appendix.

REVIEWER COMMENT:
The table suggests that patients treated with Medisorb Naltrexone 380-mg and oral naltrexone are at greater risk of suicidal ideation or suicidal attempts than are patients treated with Medisorb Naltrexone 190-mg or placebo. The data also suggest that the risk of these events is less for patients in the 380-mg group than for those in the oral naltrexone group.

The patient narratives show that the majority of subjects had a previous history of depression, anxiety, or suicide attempts/thoughts and that, with the exception of 3 cases, all events occurred more than 30 days since the last dose of study drug. This makes a causal relationship between treatment with study drug and suicide-related events less likely. Nevertheless, given that all of the cases occurred in patients treated with naltrexone (oral or depot formulations), that no placebo patients reported these adverse events, and that an association of this AE with naltrexone has been observed in previous trials, a relationship between suicide-related AEs and Medisorb Naltrexone cannot be ruled out.

**Table 7.1.3.4.2.1: Reviewer's Analysis: AEs suggestive of suicide – Studies of 4-6 months' exposure**

| SOC | Preferred Term | 190 mg N = 210 | | 380-mg N = 576 | | Oral N = 65 | | Placebo N = 214 | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % |
| Psychiatric disorders | Suicidal ideation | 2 | 0.95 | 8 | 1.39 | 2 | 3.08 | 0 | 0.0 |
| | | | | | | | | | |
| Psychiatric disorders/injury/poisoning | Suicide attempt - total | 0 | 0.0 | 5 | 0.87 | 1 | 1.54 | 0 | 0.0 |
| | Suicide attempt | 0 | 0.00 | 2 | 0.35 | 0 | 0.00 | 0 | 0.0 |
| | Non-accidental overdose [1] | 0 | 0.00 | 1 | 0.17 | 0 | 0.00 | 0 | 0.0 |
| | Intentional self-injury [2] | 0 | 0.00 | 0 | 0.00 | 1 | 1.54 | 0 | 0.0 |
| | Overdose NOS [3] | 0 | 0.00 | 2 | 0.35 | 0 | 0.00 | 0 | 0.0 |
| | | | | | | | | | |
| Injury, poisoning and procedural complications | Accidental exposure | 0 | 0.00 | 1 | 0.17 | 0 | 0.00 | 0 | 0.0 |
| | Therapeutic agent poisoning | 0 | 0.00 | 1 | 0.17 | 0 | 0.00 | 0 | 0.0 |

[1] Subject ALK21-006-252-001, gabatril overdose; [2] Subject ALK21-006-232-001; [3] Subject ALK21-006-239-016, ativan overdose

#### 7.1.3.4.2.2 Suicide-Related Events – Studies of > 6 months' exposure

Among the patients in this category of studies, I identified 7 who reported 8 suicide-related events (7/572, 1.2%). Three of the events were serious, and included a single event of completed suicide (see Sections 7.1.1 and 7.1.2.2.3.1 for details). Of note, two of the events (suicidal ideation and completed suicide) occurred in a patient (subject ALK21003-224-012) who discontinued from the 6-month study ALK21-003 and died 73 days after his last dose.

The suicide-related AEs are tabulated in the table below. I found that suicidal ideation was the most commonly reported event, occurring with the greatest frequency in patients treated with Medisorb Naltrexone 190-mg (2% vs. 0% in the other groups). The oral naltrexone group had the highest proportion of suicide attempts (3%) – however this percentage was represented by only 1 patient out of 36.

**Table 7.1.3.4.2.2: Reviewer's Analysis: Suicide related events – studies of > 6 months' exposure**

| SOC | Preferred Term | 190-mg | | 380-mg | | Oral | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Psychiatric disorders | Suicidal ideation | 3 | 1.91 | 1 | 0.26 | 0 | 0.00 |
| | Completed suicide | 1 | 0.64 | 0 | 0.00 | 0 | 0.00 |
| | | | | | | | |
| Injury, poisoning and procedural complications | Overdose NOS | 0 | 0.00 | 1 | 0.26 | 1 | 2.78 |
| | Self mutilation | 0 | 0.00 | 1 | 0.26 | 0 | 0.00 |

The narratives of the suicide-related events that I considered to be possibly related to study treatment are in the Appendix.

REVIEWER COMMENT:
The data from the studies with longer treatment exposure show that the frequency of suicide-related AEs was greater for the Medisorb Naltrexone 190-mg group. However, an association of these AEs with high-dose Medisorb Naltrexone cannot be ruled out since only interim data for two of the long-term studies (ALK21-006 and ALK21-010) were available at the time of data cut-off.

### 7.1.3.5 Allergic reactions

As mentioned in Section 7.1.3.3, the Medisorb Naltrexone database suggested that the drug may be associated with injection site reactions (ISRs) of the inflammatory type. Also, the safety database described elevations in eosinophil count, a case of eosinophilic pneumonia, and reports of rash, urticaria, and angioedema. Together, the adverse events were suggestive of an allergic reaction following study treatment.

I evaluated the frequency and severity of ISRs, pneumonia, eosinophilia, rash, urticaria and angioedema to determine whether they occurred in greater frequency among Medisorb Naltrexone patients than placebo or oral naltrexone patients. Also of concern was whether together, the demonstrated the allergenic potential of Medisorb Naltrexone.

*7.1.3.5.1 INJECTION SITE REACTIONS (ISRS)*

To assess injection tolerability, injection sites were inspected by study personnel at least monthly. Information on ISRs was collected with other physical examination observations. Investigators were to use their own judgment when determining whether or not ISRs were clinically significant. Only those reactions deemed clinically significant were considered adverse events and were recorded on the Adverse Event sheet of the CRF.

In the NDA submission, information on ISRs was contained in two datasets: the *iss-isr.xpt* and the *iss.ae.xpt* datasets. The *iss-isr.xpt* dataset comprised information an all ISRs, regardless of whether the investigator deemed them clinically significant. The *iss.ae.xpt* dataset contained information on only those ISRs that were severe enough to be recorded on the Adverse Event sheet of the CRF.

**7.1.3.5.1.1 Applicant's Analysis of ISRs – Studies of 4-6 months' exposure**

The Applicant used the *iss-isr.xpt* dataset to describe the frequency and severity of ISRs following participation in clinical trials. Alkermes found that during studies ALK21-002, ALK21-003, and ALK21-006, a total of Medisorb Naltrexone or placebo 4844 injections were administered. Approximately 55% of subjects receiving either placebo or Medisorb Naltrexone developed at least one ISR during the course of treatment. The percentage varied from 46% in the 2 mL placebo group to 88% in the 400 mg Medisorb Naltrexone group. The most common type of ISR observed was tenderness, followed by induration and pain (Table 7.1.3.5.1.1). The specific type of ISR that occurred most frequently in the Medisorb Naltrexone patients (190- or 380-mg) than in the placebo patients was injection site induration (25-29% vs. 9%).

Following an analysis of the proportion of ISRs after each monthly injection, Alkermes concluded that across all treatment groups, the frequency of ISRs declined over the course of therapy (Figure 1). Alkermes calculated that, among subjects receiving 380- or 400-mg doses of Medisorb naltrexone, the incidence of any ISR decreased from 36% after the first injection to 11% by the end of the study/data collection period.

**Table 7.1.3.5.1.1.a: Applicant's Analysis: Number (%) of subjects with ISRs – Studies of 4-6 months' exposure**

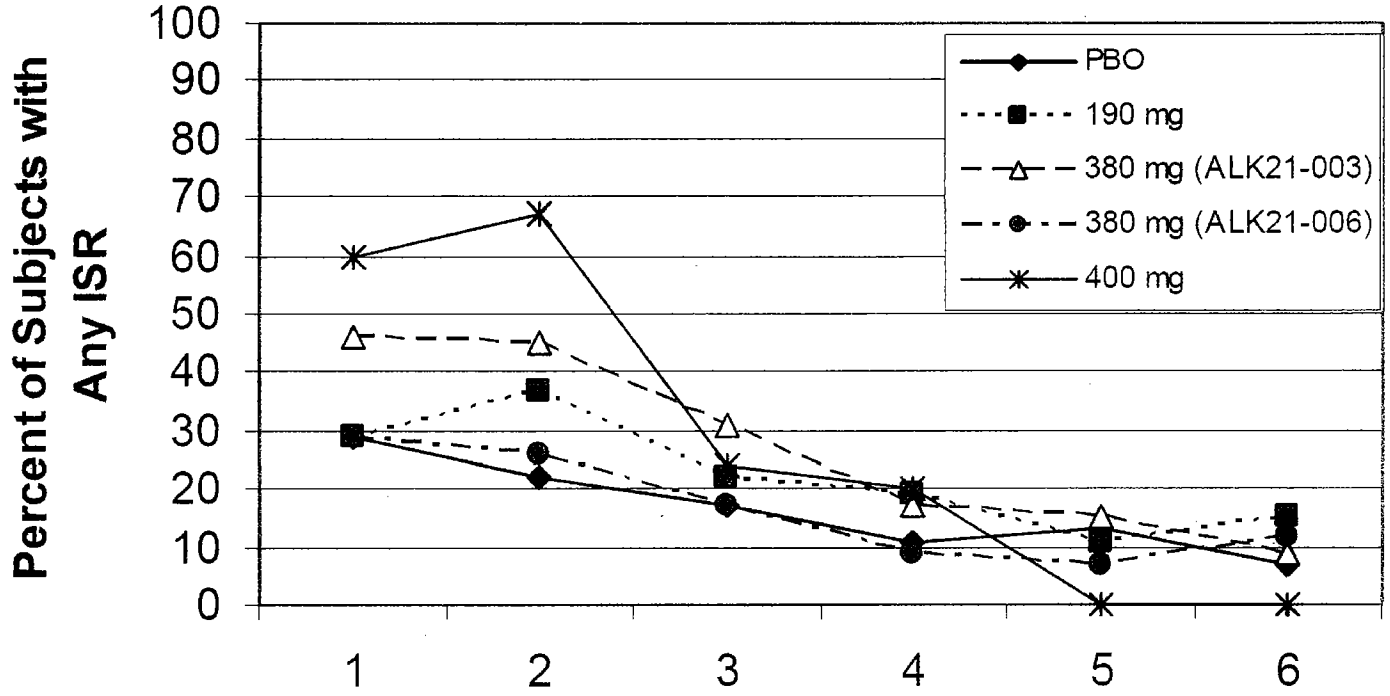
Number (%)[a] of Subjects with Injection Site Reactions(ISR)
in 4-6 Month Studies in Dependent Subjects

| Injection Site Reactions | All Subjects | Placebo (ALK21-002 & ALK21-003) | | Vivitrex | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2ml | 4ml | 190mg ALK21-003 | 380mg ALK21-003 | 380mg ALK21-006 | 400mg ALK21-002 | 380/400mg Combined |
| Number of subjects dosed | 1025 | 105 | 109 | 210 | 205 | 371 | 25 | 601 |
| No. (%)[a] of subjects with an Injection Site Reactions | | | | | | | | |
| Any ISR | 568( 55) | 48( 46) | 58( 53) | 121( 58) | 142( 69) | 177( 48) | 22( 88) | 341( 57) |
| Injection Site Tenderness | 395( 39) | 34( 32) | 49( 45) | 89( 42) | 92( 45) | 113( 30) | 18( 72) | 223( 37) |
| Injection Site Induration | 247( 24) | 8( 8) | 10( 9) | 52( 25) | 71( 35) | 99( 27) | 7( 28) | 177( 29) |
| Injection Site Pain | 93( 9) | 6( 6) | 10( 9) | 22( 10) | 34( 17) | 21( 6) | | 55( 9) |
| Injection Site Ecchymosis | 49( 5) | 8( 8) | 3( 3) | 9( 4) | 14( 7) | 15( 4) | | 29( 5) |
| Injection Site Pruritus | 47( 5) | | | 13( 6) | 21( 10) | 13( 4) | | 34( 6) |
| Other | 91( 9) | 6( 6) | 2( 2) | 16( 8) | 30( 15) | 29( 8) | 8( 32) | 67( 11) |

(Source: Applicant's Table 2.7.4.27, ISS-appendix-tables.pdf, P. 202)

APPEARS THIS WAY
ON ORIGINAL

**Figure 1: Applicant's Analysis: Injection site reactions with repeated IM administration**




| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| PBO N= | 214 | 198 | 173 | 164 | 142 | 134 |
| 190 mg N= | 210 | 187 | 169 | 156 | 144 | 137 |
| 380 mg (ALK21-003) N= | 205 | 186 | 161 | 147 | 139 | 130 |
| 380 mg (ALK21-006) N= | 371 | 330 | 300 | 277 | 252 | 232 |
| 400 mg N= | 25 | 24 | 21 | 20 | 0 | 0 |

At the Division's request, the Applicant calculated the risk of a subsequent ISR following an initial reaction at the injection site. The information was requested in order to assist with ascertainment of whether Alkermes' observation in the decline in the incidence of ISRs over time was due to true decreased risk of reaction, or whether the observed decline was driven by the population being gradually depleted of individuals prone to ISRs.

As shown in Table 7.1.3.5.1.1.b, Alkermes found that the Medisorb Naltrexone groups had a considerably higher risk of having at least 1 injection that was associated with a reaction: approximately 57% of active injections were followed by a reaction, compared to 50% of placebo injections. The risk of a second ISR after administration of at least 1 more injection was also higher for the Medisorb Naltrexone patients than the placebo patients: 60% vs. 43%. The risk of at least 1 injection or of a 2nd ISR was similar for the Medisorb Naltrexone 190-mg and 380-mg patients.

**Table 7.1.3.5.1.1.b: Frequency of experiencing subsequent ISRs after an injection associated with an ISR – Studies of 4-6 months' exposure**

| Incidence of: | All subjects | Placebo | Medisorb Naltrexone | |
|---|---|---|---|---|
| | | | 190 mg | 380/400 mg |
| At least 1 injection followed by an ISR | 568/1025 (55.4) | 106/214 (49.5) | 121/210 (57.6) | 341/601 (56.7) |
| 2nd ISR among all subjects who received at least one additional injection after the initial ISR | 297/521 (57.0) | 43/100 (43.0) | 66/110 (60.0) | 188/311 (60.5) |

Alkermes also evaluated the risk of a subsequent "clinically significant" ISR after experiencing an initial one (Table 7.1.3.5.1.1.c). Patients given Medisorb Naltrexone (either 190-mg or 380-mg) were more likely than placebo patients to experience a clinically significant ISR after at least 1 injection (14% vs. 6%). However, the risk of a second clinically significant ISR after an initial one was less (percentage-wise) for the Medisorb Naltrexone patients than for the placebo patients.

**Table 7.1.3.5.1.1.c: Frequency of experiencing subsequent "clinically significant" ISRs after an initial "clinically significant" ISR – Studies of 4-6 months' exposure**

| Incidence of: | All subjects | Placebo | Medisorb Naltrexone | |
|---|---|---|---|---|
| | | | 190 mg | 380/400 mg |
| At least 1 injection followed by a clinically significant ISR | 125/1025 (12.2) | 13/214 (6.07) | 30/210 (14.3) | 82/601 (13.6) |
| 2nd clinically significant ISR among all subjects who received at least one additional injection after the first clinically significant ISR | 33/106 (31.1) | 4/10 (40.0) | 7/25 (28.0) | 22/71 (31.0) |

The risk of a future ISR among patients who did not have a reaction following the first few injections was also explored (Table 7.1.3.5.1.1.d). The table shows that, across all groups, the

longer a subject went without experiencing an ISR, the less likely s/he was to experience an ISR with subsequent dosing.

**Table 7.1.3.5.1.1.d: Frequency "ISR-free" subjects given no previous ISRs, by dose – Studies of 4-6 months' exposure**

| No ISR associated with the $X^{th}$ dose for subjects with no previous ISR | All subjects | Placebo | Medisorb Naltrexone | |
|---|---|---|---|---|
| | | | 190 mg | 380/400 mg |
| $1^{st}$ dose | 684/1025 (66.7) | 151/214 (70.6) | 149/210 (71.0) | 384/601 (63.9) |
| $2^{nd}$ dose | 467/611 (76.4) | 115/137 (83.9) | 91/133 (68.4) | 261/341 (76.5) |
| $3^{rd}$ dose | 379/421 (91.0) | 94/102 (92.2) | 74/82 (90.2) | 211/237 (89.0) |
| $4^{th}$ dose | 335/352 (95.2) | 82/88 (93.2) | 64/68 (94.1) | 189/196 (96.4) |
| $5^{th}$ dose | 293/307 (95.4) | 63/69 (91.3) | 60/62 (96.8) | 170/176 (96.6) |
| $6^{th}$ dose | 263/273 (96.3) | 59/60 (98.3) | 54/58 (93.1) | 150/155 (96.8) |

The applicant conducted an analysis of the first 2 injections to assess the risk of future ISRs. At the 380/400 mg dose, of the 217 subjects who experienced an ISR following the first injection, 199 received a second injection, and 105 (52.8%) of these subjects had an ISR following the second injection. Of the 384 subjects who did not have an ISR following the first injection, 341 went on to receive a second injection, and 80 (23.5%) of these subjects experienced an ISR following the second injection. Therefore, for the second injection, there was a higher risk of developing an ISR when the first injection was associated with an ISR. However, almost half of the subjects who experienced an ISR following the first injection did not experience an ISR after the second injection.

Finally, Alkermes explored whether patient dropout with subsequent selective retention of only patients able to tolerate injections was the reason for the observed decline in the frequency of ISR with repeated injections. Alkermes found that in the 380/400mg group, 8.3% of the group with an ISR dropped out between the first and second dose, compared with 12.2% of the group without an ISR. Alkermes therefore concluded that a higher dropout rate does not account for this decline in ISR recurrence over time.

REVIEWER COMMENT:
The Applicant's analyses show that injection with Medisorb Naltrexone has a higher risk of an associated ISR than injection with placebo. Among patients who experience an ISR with the initial injection, the risk of a subsequent ISR is also greater with Medisorb Naltrexone treatment than with placebo treatment. However, there does not appear to be an increased risk of a subsequent "clinically significant" ISR following an initial one among patients administered Medisorb Naltrexone. Also, longer a patient goes without having an ISR with repeated injections, the less likely they will experience an injection-related reaction.

Nevertheless, there is a 25% chance of having an ISR after a $2^{nd}$ injection even if there was no reaction after the first. And about one third of patients who have a clinically significant reaction on initial injection will have another clinically significant ISR on subsequent injection.

#### 7.1.3.5.1.2 Reviewer's Analysis of ISRs

Using both the *iss-isr.xpt* and *iss-ae.xpt* datasets, I also evaluated the overall frequency of reactions related to study drug administration, specifically injection site reactions.

**Reviewer's Analysis of ISRs – Using the *iss-isr.xpt dataset***

**Studies of 4-6 months' exposure**

Excluding the 65 patients in Study ALK21-006 who were treated with oral naltrexone, a total of 1025 patients were administered at least one injection. I found that of these 1025 patients, there were 568 (55.4%) who experienced one or more injection site reactions. The frequency of ISRs was greatest in the Medisorb Naltrexone 400-mg group (88%), and lowest in the placebo 2-mL group (46%). Overall, however, the frequency of ISRs was considerably greater in the Medisorb Naltrexone groups than in the placebo groups.

**Table 7.1.3.5.1.2.a: Frequency (N, %) of ISRs by treatment group – Studies of 4-6 months' exposure**

| 2 mL PBO N = 105 | 4 mL PBO N = 109 | Pooled PBO N = 214 | 190 mg N = 210 | 380 mg N = 576 | 400 mg N = 25 | 380/400 mg N = 601 |
|---|---|---|---|---|---|---|
| 48 (45.7%) | 58 (53.2%) | 106 (49.5) | 121 (57.6%) | 319 (55.4%) | 22 (88%) | 341 (56.7%) |

The majority of patients reported 1-2 injection site reactions. The maximum number of ISRs reported by a single patient was 13.

**Table 7.1.3.5.1.2.b: Number ISRs per patient – Studies of 4-6 months' exposure**

| Number of Injection Site Reactions | Number of Patients |
|---|---|
| 1 | 210 |
| 2 | 141 |
| 3 | 89 |
| 4 | 57 |
| 5 | 37 |
| 6 | 15 |
| 7 | 7 |
| 8 | 6 |
| 9 | 3 |
| 10 | 2 |
| 13 | 1 |

A total of 4844 injections were administered during the 4-6 month trials, and 1419 ISRs were reported in the *iss-isr.xpt* dataset. Of these 1419 ISRs, the study investigators considered 231 to be "clinically significant." The proportions of clinically significant reactions by treatment group are shown below. Approximately 2 times fewer placebo patients (6%) than Medisorb Naltrexone patients (14%) were likely to experience a "clinically significant" ISR.

**Table 7.1.3.5.1.2.c Frequency (N, %) of "clinically significant ISRs by treatment group – Studies of 4-6 months' exposure**

| 2 mL PBO N = 105 | 4 mL PBO N = 109 | Pooled PBO N = 214 | 190 mg N = 210 | 380 mg N = 576 | 400 mg N = 25 | 380/400 mg N = 601 |
|---|---|---|---|---|---|---|
| 6 (5.8%) | 7 (6.4%) | 13 (6.1%) | 30 (14.3%) | 77 (13.4%) | 5 (20.0%) | 82 (13.6%) |

The types of ISRs (whether "clinically significant" or not) are listed in the table that follows. Injection site tenderness was the most frequently reported type of ISR, occurring with greatest frequency in the 400-mg Medisorb Naltrexone patients. However, when the 380-mg and 400-mg groups were combined, the frequency of tenderness was comparable across the active and placebo groups. Injection site induration was the next most common type of ISR, occurring approximately three times (3x) more frequently in the Medisorb Naltrexone patients than the placebo patients. Also more likely to be reported in the Medisorb groups were injection site pain, pruritus, and "other" reactions.

**Table 7.1.3.5.1.2.d: Types of ISRs by treatment group – Studies of 4-6 months' exposure**

| Type of ISR | Placebo | | | | | | Medisorb Naltrexone | | | | | | | | All subjects N=1025 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 mL N = 105 | | 4 mL N = 109 | | Pooled N = 214 | | 190 mg N = 210 | | 380 mg N = 576 | | 400 mg N = 25 | | 380/400 N = 601 | | | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Tenderness** | 34 | 32.38 | 49 | 44.95 | 83 | 38.79 | 89 | 42.38 | 205 | 35.59 | 18 | 72.00 | 223 | 37.10 | 395 | 38.54 |
| **Induration** | 8 | 7.62 | 10 | 9.17 | 18 | 8.41 | 52 | 24.76 | 170 | 29.51 | 7 | 28.00 | 177 | 29.45 | 247 | 24.10 |
| **Pain** | 6 | 5.71 | 10 | 9.17 | 16 | 7.48 | 22 | 10.48 | 55 | 9.55 | 0 | 0.00 | 55 | 9.15 | 93 | 9.07 |
| **Other** | 6 | 5.71 | 2 | 1.83 | 8 | 3.74 | 16 | 7.62 | 59 | 10.24 | 8 | 32.00 | 67 | 11.15 | 91 | 8.88 |
| **Echymosis** | 8 | 7.62 | 3 | 2.75 | 11 | 5.14 | 9 | 4.29 | 29 | 5.03 | 0 | 0.00 | 29 | 4.83 | 49 | 4.78 |
| **Pruritus** | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 13 | 6.19 | 34 | 5.90 | 0 | 0.00 | 34 | 5.66 | 47 | 4.59 |

A total of 91 patients described 116 "other" types of ISRs. The verbatim descriptions of these reactions were reviewed and the number of these reactions ascertained (Table 7.1.3.5.2.e). Injection site nodules and or lumps were the most common type of reaction labeled as "other." Also predominant in this subset of ISRs was swelling at or around the site, discoloration, and rash. One patient had leakage of a considerable amount of study drug from the injection site.

**Table 7.1.3.5.1.2.e: Specific descriptions of ISRs coded as "other" – Studies of 4-6 months' exposure**

| Description of reaction | Number of reports |
|---|---|
| Nodule | 23 |
| Swelling | 20 |
| Lump/knot/mass | 17 |
| Redness/erythema/discoloration | 15 |
| Rash at injection site/generalized hives | 11 |
| Stinging/hyperesthesia/sensitivity | 8 |
| Warmth/heat | 7 |
| Bleeding/hematoma | 3 |
| Inflammation | 3 |
| Numbness | 3 |
| Tissue necrosis | 1 |
| Poor healing ("won't scab over") | 1 |
| Varicosity | 1 |
| Pain during injection | 1 |
| Leakage of drug ("orange cylindrical plug of material, ~ 2mm x 20 mm gelatinous discharge from injection site) | 1 |

Among the studies of 4-6 months' exposure, the median duration of an ISR was 6 days and the mean duration was 16.5 days (range: 0 days to 196 days). Reactions considered to be "clinically significant" had a slightly prolonged median duration: 8 days (mean = 22 days; range 0 to 181 days). The median duration of an ISR increased with increasing dose of Medisorb Naltrexone: 5 days for the 190-mg patients, 7 days for the 380-mg patients, and 10 days for the 400-mg patients. The placebo group had the shortest median ISR duration – 3 days.

REVIEWER COMMENT:
Overall, the information from the *iss-isr.xpt* dataset shows that treatment with Medisorb Naltrexone is associated with a greater frequency of injection site reactions than treatment with placebo. Medisorb Naltrexone injections are more likely than placebo injections to yield "clinically significant" reactions. The types of reactions common with Medisorb Naltrexone injections suggest an inflammatory type reaction, with tenderness, induration, erythema, and heat. Rash and pruritus are also observed, which are concerning for an allergic response. In general, injections are of relatively short duration (on the order of days); however, reactions lasting months are not unusual. Also, the higher the dose of Medisorb Naltrexone, the longer the ISR will last.

**Reviewer's Analysis of ISRs – Using the *iss-ae.xpt dataset***

As mentioned in Section 7.1.3.5, this dataset contained information on only those ISRs that investigators considered severe enough to record as an adverse event following drug administration.

Remaining blind to treatment assignment, I used the *iss-ae.xpt* dataset, I first identified all body system (i.e. System Organ Class) terms that might capture an injection-related AE[8]. I then searched by High Level Terms for the AEs that more clearly suggested an injection site reaction[9]. Finally, I selected AEs that contained the word "injection" in either the verbatim term, or in the Lower Level Term that contained the terms "ISR" or "injection."

I found that 132 patients reported 236 occurrences of injection-related AEs. The majority of these AEs were categorized as "general disorders and administration site conditions" (n = 230), and the rest were described as skin and subcutaneous tissue disorders (n = 4), and "musculoskeletal and connective tissue disorders" (n = 2). Included in the 236 reports were two non-serious cases of rash on the buttocks that, per the verbatim terms, were not in the vicinity of the injection site[10]. These patients were removed from the analysis of ISRs. Therefore, there were 130 patients who reported 234 injection-related AEs.

The table below shows my calculation of the frequency of injection-related AEs. Overall, the types of AEs suggest that administration of study medication was associated with an inflammatory-type reaction, with redness, swelling, and discomfort. "Injection site pain" was the most frequently occurring ISR for all treatment groups, and was considerably more frequent in the high dose groups (~ 16%) than in the Medisorb Naltrexone 190-mg group (10%) and the placebo (7%) group. Although one patient (ALK21003-202-003, placebo) reported "pain in limb," review of the verbatim term found that the patient experienced non-serious pain in his limb due to an unspecified injection site reaction.

The next most commonly occurring type of ISR was "injection site induration." Again, induration was most frequent in the 380-mg and 400-mg groups (~ 7% to 9%), than in the 190-mg (4%) and placebo groups (3%). Other terms consistent with induration were "injection site mass" (n = 5), "injection site swelling" (n = 1). Combining these AEs with the reports of injection site indurations found that again, this type of reaction was most common in the high dose groups.

Changes in skin color at the site of the injection were the next most frequent type of ISR, and were described as "erythema," "bruising," "and inflammation." Skin color changes were more common among patients treated with 380-mg (1.6%, 9/576) than in placebo patients (0.5%, 1/214), but only slightly higher than in patients treated with 190-mg (1.0%, 2/210).

[8] These terms included "surgical and medical procedures;" "skin and subcutaneous tissue disorders;" "musculoskeletal and connective tissue disorders;" "injury, poisoning and procedural complications;" and "general disorders and administration site conditions."

[9] The High Level Terms were "dermal and epidermal conditions NEC;" "device related complications;" "discomfort NEC;" "injection site reactions;" "maladministration and accidental exposure;" "muscle pains;" "muscle related signs and symptoms NEC;" "muscle, tendon, and ligament injuries;" "musculoskeletal and connective tissue signs and symptoms;" "non-site specific injuries NEC;" "non-site specific procedural complications;" "pains NEC;" "pruritus;" "rashes, eruptions and exanthems;" "site specific injuries;" "skin and subcutaneous tissue ulcerations;" " skin injuries NEC;" and "skin injuries and mechanical dermatoses."

[10] Subjects ALK21003-202-004 and ALK21003-212-002

ISRs that are of concern are "necrosis," "hemorrhage," "granuloma," and "hypersensitivity," and "cyst." (n = 1, each)[11]. Only the case of injection site necrosis (subject ALK21006-246-013, 380-mg) was labeled as serious (see Section 7.1.2.2.4). Patient narratives and CRFs for the remaining non-serious cases were provided at the Agency's request. Review of these data found that the events *were* related to drug administration. However, each event was mild, resolved within days, had no adverse consequences, and did not lead to study discontinuation.



11 Subject ALK21003-211-001: hypersensitivity; Subject ALK21006-237-002: hemorrhage; Subject ALK21006-241-024: granuloma; Subject ALK21006-255-020: injection site cyst

**Table 7.1.3.5.1: Reviewer's Analysis: Frequency of Injection Site Reactions in 4-6 month trials**

| Body System | Preferred Term | All Pts | | 380/400 mg Combined N = | | ALK 002 400 mg N = | | ALK 003 380 mg N = | | ALK 006 380 mg N = | | ALK 003 190mg N = | | Placebo N = | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| General disorders and administration site conditions | Injection site pain | 110 | | 75 | 12.48 | 4 | 16.00 | 34 | 16.59 | 37 | 9.97 | 20 | 9.52 | 15 | 7.01 |
| | Injection site induration | 53 | | 39 | 6.49 | 2 | 8.00 | 19 | 9.27 | 18 | 4.85 | 8 | 3.81 | 6 | 2.80 |
| | Injection site pruritus | 15 | | 9 | 1.50 | 0 | 0.00 | 7 | 3.41 | 2 | 0.54 | 6 | 2.86 | 0 | 0.00 |
| | Injection site inflammation | 7 | | 6 | 1.00 | 0 | 0.00 | 4 | 1.95 | 2 | 0.54 | 1 | 0.48 | 0 | 0.00 |
| | Injection site edema | 9 | | 6 | 1.00 | 0 | 0.00 | 6 | 2.93 | 0 | 0.00 | 3 | 1.43 | 0 | 0.00 |
| | Injection site reaction NOS | 6 | | 5 | 0.83 | 0 | 0.00 | 2 | 0.98 | 3 | 0.81 | 1 | 0.48 | 0 | 0.00 |
| | Injection site bruising | 8 | | 4 | 0.67 | 0 | 0.00 | 1 | 0.49 | 3 | 0.81 | 4 | 1.90 | 0 | 0.00 |
| | Injection site erythema | 3 | | 3 | 0.50 | 0 | 0.00 | 0 | 0.00 | 3 | 0.81 | 0 | 0.00 | 0 | 0.00 |
| | Injection site rash | 5 | | 3 | 0.50 | 0 | 0.00 | 2 | 0.98 | 1 | 0.27 | 1 | 0.48 | 1 | 0.47 |
| | Injection site mass | 5 | | 2 | 0.33 | 0 | 0.00 | 2 | 0.98 | 0 | 0.00 | 3 | 1.43 | 0 | 0.00 |
| | Injection site burning | 2 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 1 | 0.48 | 0 | 0.00 |
| | Injection site cyst | 1 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 0 | 0.00 | 0 | 0.00 |
| | Injection site granuloma | 1 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 0 | 0.00 | 0 | 0.00 |
| | Injection site hemorrhage | 1 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 0 | 0.00 | 0 | 0.00 |
| | Injection site necrosis | 1 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 0 | 0.00 | 0 | 0.00 |
| | Injection site swelling | 1 | | 1 | 0.17 | 0 | 0.00 | 0 | 0.00 | 1 | 0.27 | 0 | 0.00 | 0 | 0.00 |
| | Injection site hypersensitivity | 1 | | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 | 0.48 | 0 | 0.00 |
| | | | | | | | | | | | | | | | |
| Musculoskeletal and connective tissue disorders | Pain in limb | 2 | | 1 | 0.17 | 0 | 0.00 | 1 | 0.49 | 0 | 0.00 | 0 | 0.00 | 1 | 0.47 |
| | | | | | | | | | | | | | | | |
| Skin and subcutaneous tissue disorders | Contusion | 2 | | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 2 | 0.93 |

*7.1.3.5.2 EOSINOPHILIA*

Applicant's evaluation of Eosinophilia

*Applicant's s analysis - Study ALK21-003*
In Study ALK21-003, no significant group changes were noted for any hematology parameter except eosinophil count. By Day 28 (week 4), the eosinophil count had risen by a mean of 0.021 (x $10_3/\mu L$) for placebo subjects, 0.065 for subjects in the Medisorb Naltrexone 190 mg group, and by 0.091 for subjects in the Medisorb Naltrexone 380mg group. No further increases in the Medisorb Naltrexone group occurred after Week 4, but group mean eosinophil counts remained elevated for the remainder of the study. This increase in eosinophil count, although statistically significant, was not numerically sizeable. Nevertheless, is suggests an allergic response to study drug, with greater responses at increasing doses of Medisorb Naltrexone.

AEs of increased eosinophil count were reported by 4 subjects; 2 in the Medisorb Naltrexone 380 mg group, 1 in the Medisorb Naltrexone 190 mg group, and 1 in the placebo group. However, overall at Week 24 there were 21 patients with high eosinophil counts: 3 (1.4%) patients in the placebo group, 5 (2.4%) in the 190-mg group, and 13 (6.3%) in the 380-mg group. For the most part, these increases were moderately above the upper limit of normal.

*Applicant's analysis - All studies*
Eosinophil counts were evaluated for individual trials, as well as for the 4-6 month and > 6 months categories of trials. In study ALK21-006, similar differences were seen between the oral naltrexone group and those subjects who were administered Medisorb Naltrexone. Data from trials of > 6 months of exposure showed that mean eosinophil counts tended to return to normal with continued exposure to treatment.

> REVIEWER COMMENT:
> Alkermes' findings from Study ALK21-003 suggest that Medisorb Naltrexone treatment is associated with elevations in eosinophils, possibly as a result of an allergic reaction to the injection. However, in the absence of other data, reactions to other allergens cannot be ruled out. Given the finding that patients treated with oral naltrexone showed similar changes in eosinophil count as Medisorb Naltrexone patients, the increase in eosinophil counts may reflect an allergic response to the active moiety, naltrexone, and is therefore independent of drug formulation. The observation that long-term studies did not show a progressive increase in eosinophil count, suggests that the response does not worsen with repeated treatment.

Reviewer's evaluation of Eosinophilia
Using the *iss_lab2.xpt* dataset, I determined the mean change, the shifts, and marked outliers in eosinophils for the 4-6 month trials.

*Reviewer's analysis: Measures of central tendency*

I found that, with the exception of the oral naltrexone group, all of the treatment groups showed a slight increase in the mean eosinophil levels at Week 24. The increase was largest for the Medisorb Naltrexone 190-mg group and lowest for the placebo group.

**Table 7.1.3.5.2.a: Mean change in eosinophils, from baseline to week 24 – Studies of 6 months' exposure**

| Eosinophils (x $10^3$/uL) | Placebo | Medisorb naltrexone | | Oral NTX |
|---|---|---|---|---|
| | | 190 mg | 380/400 mg* | |
| Mean, baseline | 0.17 | 0.17 | 0.18 | 0.17 |
| Mean, Wk 24 | 0.19 | 0.22 | 0.22 | 0.14 |
| Mean change from BL to Wk 24** | 0.01 | 0.06 | 0.03 | -0.03 |

* Patients were treated with Medisorb Naltrexone 400-mg in Study ALK21-002 only. Since this was a 4-month (i.e. 16-week trial, there were no data at 24 weeks for the 400-mg patients, and all of the data in the combined group were from the 380-mg patients.
** Mean change was calculated by summing the change from baseline for each individual patient, and then dividing by the total number of patients

*Reviewer's analysis: Shifts from normal to abnormal*

Shifts from the normal to the high range, from baseline to Week 24, are shown below. Again, all groups, except the oral naltrexone group, showed a shift in eosinophil values from baseline to Week 24. The Medisorb Naltrexone 190-mg group had the highest proportion of patients who shifted from normal to high (4%), followed by the 380-mg group (3%) and the placebo group (2%). Thus, the risk of going from a normal eosinophil count at baseline to a high one following Medisorb Naltrexone treatment was approximately twice that of placebo treatment. One patient (in the 380-mg arm) had an increase in eosinophils to at least 3x the upper limit of normal.

**Table 7.1.3.5.2.b: Shift table for eosinophils, from normal to high – Studies of 6 months' exposure**

| Eosinophil shifts | Placebo Baseline N = 214 Week 24 N = 120 | Medisorb NTX | | Oral NTX Baseline N = 65 Week 24 N = 36 |
|---|---|---|---|---|
| | | 190-mg Baseline N = 209 Week 24 N = 118 | 380-mg Baseline N = 574 Week 24 N = 320 | |
| *Shifts from normal (BL) to high (Wk 24)* | | *N (%)* | | |
| | 2 (1.6) | 5 (4.2) | 9 (2.8) | 0 (0) |
| | | | | |
| Shifts from normal (BL) to 3x ULN (Wk 24) | | N (%) | | |
| | 0 (0) | 0 (0) | 1 (0.3) | 0 (0) |

*Reviewer's analysis: marked outliers and dropouts for eosinophil abnormalities*

*Eosinophil elevations to at least 3x ULN*

As indicated in the table above, one patient had an increase in eosinophils to at least 3x ULN (subject ALK21003-215-018, Medisorb Naltrexone 380-mg). This 41 year old male patient completed the efficacy study, and continued treatment in open-label studies. During the first 6 months of treatment the eosinophil count progressively increased, until its maximum at Month 6. Reported AEs during that time were influenza and a myocardial infarction of indeterminate age. Almost 18 months after the first dose of study drug, during open label treatment, the patient experienced a hypersensitivity reaction (verbatim term: "allergies"). His eosinophil count 2 weeks prior to the event had been 0.68 x $10^3$/uL, which was only slightly outside of the normal

reference range. Otherwise, over the course of open-label therapy, the patients eosinophil count was variably elevated (0.66 to 1.41 x $10^3$/uL). However, the count normalized over the final 8 weeks of observation.

**Table 7.1.3.5.2.c: Subject ALK21003-215-018: Monthly eosinophil values**

| Visit | Value (x $10^3$/uL)* | Change from BL | |
|---|---|---|---|
| Baseline (BL) | 0.36 | - | |
| Week 4 | 0.60 | 0.24 | Double blind |
| Week 8 | 0.79 | 0.43 | |
| Week 12 | 0.79 | 0.43 | |
| Week 16 | 0.70 | 0.34 | |
| Week 20 | 0.45 | 0.09 | |
| Week 24 | 3.20 | 2.84 | |
| Week 32 | 1.41 | 1.05 | Open label |
| Week 40 | 0.90 | 0.54 | |
| Week 52 | 0.58 | 0.22 | |
| Week 64 | 1.18 | 0.82 | |
| Week 76 | 0.68 | 0.32 | |
| Week 84 | 0.66 | 0.3 | |
| Week 92 | 0.13 | -0.23 | |
| Week 100 | 0.22 | -0.14 | |

*Normal range for eosinophils: 0-0.5 x $10^3$/uL

REVIEWER COMMENT: Overall, this patient showed an elevation of eosinophils with continued exposure to Medisorb Naltrexone. The reason for the maximum elevation at Month 6 is unclear. There were no other reported events that could explain the rise in eosinophils, other than treatment with Medisorb Naltrexone.

*Dropouts due to eosinophilia*

Two patients were listed as discontinuing study drug due to eosinophilia. All were treated with Medisorb Naltrexone at the time of the AE. Their eosinophil counts are listed in the table that follows.

Subject ALK21003-202-019 participated in 3 trials: in the first he was given Medisorb Naltrexone 380-mg for 4 months; in the second he was treated with placebo for 6 months; and in the third he received a 4 dose of 380-mg prior to discontinuation. This patient's eosinophil count was within normal limits during the initial 2 trials, but was elevated by the time of first laboratory assessment of the 3rd trial. Of note, approximately 2 months prior to the eosinophilia, the patient had been bitten by an insect. Thus, there is a possible alternate cause for the observed increase in eosinophil count.

Subject ALK21003-212-009 prematurely withdrew from Study ALK21-003 after 5 doses of study drug. Eosinophil elevations were noted during routine laboratory assessments taken when the 3rd dose was administered, however results were not available until after the 4th dose was given. Despite continued elevations noted at the time of the 4th dose, a 5th dose was given. When elevations persisted, the patient discontinued treatment.

**Table 7.1.3.5.2.d: Monthly eosinophil values for patients described as discontinuing due to eosinophilia**

| Patient ID | Treatment group at D/C | # study doses prior to D/C | Eosinophil count | | | Comments |
|---|---|---|---|---|---|---|
| | | | Study/ Dose | Visit | Count | |
| ALK21003-202-019 | 380-mg | 10 | Alk21-002 380-mg | BL | 0.2 | Eosinophilia noted 5/22/03. Pt had arthropod bite 2/13/03. Neutrophilia (7/10/03), leucocytosis (7/10/03) and lymphocytosis (8/1/03) also noted. |
| | | | | Wk 4 | 0.3 | |
| | | | | Wk 8 | 0.3 | |
| | | | | Wk 12 | 0.3 | |
| | | | | Wk 16 | 0.3 | |
| | | | | Wk 20 | 0.3 | |
| | | | Alk21-003 Placebo | BL to Wk 24 | 0.25 to 0.54 | |
| | | | Alk21-003X 380-mg | Wk 32 | 0.9 | |
| | | | | | | |
| ALK21003-212-009 | 380-mg | 5 | Alk21-003 380-mg | BL | 0.21 | There were no reported AEs at the time of eosinophil elevation that might explain the abnormal results. |
| | | | | Wk 4 | 0.63 | |
| | | | | Wk 8 | 0.35 | |
| | | | | Wk 12 | 0.89 | |
| | | | | Wk 16 | 0.74 | |

REVIEWER COMMENT:
Overall, very few patients dropped out of the studies due to eosinophil abnormalities. Both of the discontinuations occurred in patients given Medisorb Naltrexone 380-mg, and none were in placebo treated patients. None of the discontinuants had excessive increases in eosinophil count. Thus, the data are not overwhelming for eosinophilia being a major treatment-limiting factor.

### *7.1.3.5.3 URTICARIA/ANGIOEDEMA*

I found that 15 patients in total reported urticaria (n = 10) and/or angioedema (n = 7) during the trials with Medisorb Naltrexone. Twelve patients had urticaria/angioedema following 4-6 months' exposure, and 3 patients had these AEs following > 6 months of drug exposure. The cases of urticaria were described as hives (either generalized or localized), or "rash with urticaria." The cases of angioedema were localized to the face and included swelling of the lips, as well as "face edema." Two of the patients had an alternate cause for their symptoms (namely sulfa drug allergy). The events are summarized in Table 7.1.3.5.3.b.

Among participants the trials of 4-6 months' exposure, there were 12 patients who had urticaria (n = 8) and/or angioedema (n = 5). There were no reports of angioedema or urticaria in placebo- or oral naltrexone-treated patients. The frequency of these AEs during the 4-6 month studies is

shown below (by treatment group). The risk of urticaria and/or angioedema was slightly greater for the combined Medisorb Naltrexone patients compared to the placebo-treated patients. The risk of the AEs did not appear to increase with increasing dose of Medisorb Naltrexone; rather, the greatest frequencies were reported in the 190-mg group compared to the 380-mg and 400-mg groups.

**Table 7.1.3.5.3.a: Frequency of urticaria and/or angioedema – Studies of 4-6 months' exposure**

| | Placebo N = 214 | 190-mg N = 210 | 380-mg N = 576 | 400-mg N = 25 | 380/400 mg N = 601 | All N = 811 |
|---|---|---|---|---|---|---|
| Angioedema | 0 (0%) | 2 (1.0%) | 2 (0.3%) | 1 (4.0%) | 3 (0.5%) | 5 (0.6%) |
| Urticaria | 0 (0%) | 4 (1.9%) | 4 (0.7%) | 0 (0.0%) | 4 (0.7%) | 8 (1.0%) |

As shown in Table 7.1.3.5.3.b (following page), there were 2 patients who experienced angioedema (n = 1) or urticaria (n = 1) after within days of their initial injection of Medisorb Naltrexone. The majority of patients, however, first experienced symptoms after more than 1 injection. Four patients had recurrent/ongoing symptoms with repeated injections. Three patients discontinued due to their adverse event (1 in the 4-6 month trials). Patients' symptoms generally lasted no more than 1-2 weeks; however, some patients (most of whom had multiple injections) had symptoms that lasted for months. Patients who were administered with antihistamines and other anti-allergy medications responded well to treatment. No patients required epinephrine.

**Table 7.1.3.5.3.b – Description of events of angioedema and/or urticaria**

| Subj ID | AE/Reaction | Dose group at AE onset | Dose group in blinded study | # injections at AE onset | Interval last dose to AE onset | Interval first dose to AE onset | Reaction duration | Discontinued due to AE | # subsequent injections | Reaction after additional injections | Other likely cause |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Studies of 4-6 months' exposure*** | | | | | | | | | | | |
| ALK21-002-202-016 | Angioedema (lip & eye swelling, w/ peri-oral pruritus | 400-mg | 400-mg | 2 | 12 days | 38 days | 13 days | Yes | 0 | N/A | No |
| ALK21-003-202-004 | Angioedema (lip and tongue edema) | 380-mg | 380-mg | 6 | 4 days | 209 days | 5 hours | No | 0 | N/A* | No |
| ALK21-003-217-029 | Urticaria (generalized hives) | 190-mg | 190-mg | 6 | 10 days | 150 days | 3 days | No | 0 | N/A* | No |
| ALK21-003-217-030 | Urticaria (generalized hives) | 190-mg | 190-mg | 3 | 12 days | 74 days | 1 days | No | 3 | No | No |
| ALK21-003-224-026 | Urticaria (hives on upper body)<br>Angioedema (lip swelling) | 190-mg | 190-mg | 6 | 7 days | 146 days | 4 days | No | 0 | N/A* | No |
| ALK21-003-217-003 | Urticaria | 380-mg | 380-mg | 4 | 9 days | 100 days | 6 days | No | 2 | No | No |
| ALK21-003-225-016 | Angioedema (lip swelling) | 190-mg | 190-mg | 1 | 2 days | 2 days | 6 hours | No | 4 | No | No |
| ALK21-003-227-006 | Urticaria (hives) | 190-mg | 190mg | 6 | 18 days | 157 days | 3 days | No | 0 | N/A* | Yes (sulfa drug) |
| ALK21-006-237-010 | Urticaria (hives) | 380-mg | 380-mg | 5 | 24 days | 136 days | Ongoing after 300 days | No | 8 | Yes (hives) | No |

**Table 7.1.3.5.3.b – Description of events of angioedema and/or urticaria** (continued)

| Subj ID | AE/Reaction | Dose group at AE onset | Dose group in blinded study | # injections at AE onset | Interval last dose to AE onset | Interval first dose to AE onset | Reaction duration | Discontinued due to AE | # subsequent injections | Reaction after additional injections | Other likely cause |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Studies of 4-6 months' exposure*** | | | | | | | | | | | |
| ALK21-006-245-014 | Urticaria (rash) | 380-mg | 380-mg | 2 | 11 days | 37 days | Ongoing after 250 days | No | 4 | Yes (urticaria, lip swelling) | Yes (sulfa drug) |
| | Angioedema (facial edema) | | | 6 | 32 days | 194 days | Ongoing after 93 days | No | 1 | Unknown (subject lost to F/U) | No |
| ALK21-006-250-013 | Urticaria (hives on the neck) | 380-mg | 380-mg | 1 | 18 days | 18 days | 4 days | No | 5 | No | No |
| ALK21-003-006-250 | Angioedema (lip swelling) | 380-mg | 380-mg | 3 | 4 days | 62 days | 1 days | No | 1 | Yes (angioedema – lip swelling) | No |
| | Angioedema (lip swelling) | | | 4 | 2 days | 116 days | Hours | No | 1 ** | No | No |
| ***Studies of > 6 months' exposure*** | | | | | | | | | | | |
| ALK21-006-214-011 | Urticaria (hives) | 380-mg | 380-mg | 8 | 12 days | 233 days | 13 days | No | 1 | Yes (urticaria, hives) | No |
| | Urticaria (hives) | | | 9 | 7 days | 245 days | Ongoing after 178 days | No | 5 | No | No |
| ALK21-010-209-015 | Urticaria (hives at lower leg) | 380-mg | 380-mg | 19 | 9 days | 515 days | 48 days | No | 17 | No | No |
| ALK21-003EXT-212-003 | Urticaria (hives at injection site) | 190-mg | 190-mg | 7 | 1 day | 180 days | 4 days | Yes | 0 | N/A | No |
| | Urticaria (hives at right hip, lower torso) | | | | 8 days | 187 days | Ongoing (at time of discontinuation) | Yes | | | |

* No further doses were given since the subject had completed the 6-month trial
** Subject withdrew from the study due to an AE of ischemic stroke

REVIEWER COMMENT:
The cases of angioedema and urticaria, in the absence of an alternate cause, are strongly indicative of an allergic or sensitivity reaction following treatment to study drug. Since no placebo or oral naltrexone patients developed urticaria and/or angioedema, the observed reactions were likely due to the Medisorb Naltrexone. Overall, very few patients in the population experienced this reaction and only slightly more patients in the Medisorb Naltrexone arms described angioedema/urticaria than did placebo patients.

Given that Medisorb Naltrexone is a depot that continually releases drug over a period of weeks, it is important to identify risk factors for an allergic reaction. However, the events occurred at varying intervals from administration of the first dose, at varying intervals from the most recent dose, and after one or multiple doses. Also, symptoms were noted in patients with or without a history of allergies. Consequently, prediction of patients at risk for an allergic reaction is difficult. In addition, although no serious cases were reported, due to the small number of reported events, no firm conclusions can be made regarding the risk of a severe reaction.

*7.1.3.5.4 RASH*

Using data from trials ALK21-002, -003, and -006, I found 66 patients (66/1090, 6%) who reported the following skin-related HLTs: rash; erythema; urticarias, exfoliative conditions; papulosquamous conditions; photosensitivity conditions; dermatitis and eczema; dermal and epidermal conditions; rashes, eruptions, and exanthems, and skin and subcutaneous tissue ulcerations.

Of these AEs, rash ("rash NOS," (n=35) and 'rash papular," (n=4)) was the most common (39/1090, 3.5%), followed by dermatitis (10/1090, 1%) and urticaria (0.7%). The frequency of rash was greatest for the Medisorb Naltrexone 400-mg patients (3/25, 12%), but was otherwise similar across the 190-mg, 380-mg, oral naltrexone, and placebo groups (~ 3-4%). There were no serious or severe cases of rash; cases were either mild or moderate.

REVIEWER COMMENT: The data show that although some patients reported rash, the cases were usually mild or moderate, and the frequency of events in the Medisorb Naltrexone patients was similar to that in the placebo group.

*7.1.3.5.5 PNEUMONIA*

See Section 7.1.2.2.3.3.

*7.1.3.5.6 ALLERGY CONSULT REGARDING ALLERGENEITY OF MEDISORB NALTREXONE*

Dr. Charles Lee in the Division of Pulmonary and Allergy Products reviewed the data on the serious injection site reaction, eosinophilic pneumonia, eosinophilia, angioedema and urticaria. The likelihood of an association with medication was considred separately for each adverse event.

Dr. Lee concluded that the data are insufficient to fully ascertain whether the single serious ISR case was the result of an immune reaction. The data are insufficient to determine the mechanism of action for the reaction, as well as possible predictive factors to identify patients at risk for such reactions.

Dr. Lee found that the reports of serious pneumonia were consistent with eosinophilic pneumonia. Eosinophilic pneumonia can be drug-induced, however a mechanism for the events following Medisorb Naltrexone administration can't be elucidated from the data. The incidence of this usually uncommon condition in the clinical trials is concerning, particularly since the patient population (i.e. alcoholoics) is especially vulnerable and may not recognize preceding pulmonary symptoms as serious and requiring medical attention.

Dr. Lee found that, in isolation, the findings of elevated levels of eosinophils were concerning. However, given that eosinophilia resolved with continued dosing for many patients, a causative and worrisome association with Medisorb Naltrexone treatment cannot be made.

Dr. Lee considered that the most supportive evidence of allergenity of Medisorb Naltrexone came from the reports of urticaria and angioedema. The relatively large number of reports, as well as the lack of cases among placebo patients strongly indicated an association with active treatment. However, because the data showed that some patients were able to tolerate further dosing and there were no serious cases, a hypersensitivity reaction is less likely.

Dr. Lee theorized that perhaps the symptoms and signs were due to non-specific mast cell degranualtion and not necessarily to an IgE-mediated hypersensitivity process. Other drugs such as opioids, IV contrast materials, and vancomycin are known to cause 'allergic' reactions due to mast cell degranulation. However, a hypersensitivity response to naltrexone or the carboxymethylcellulose excipient in Medisorb Naltrexone cannot be ruled out.

Overall, therefore, the available information does not allow for determination of the mechanism for the various observed adverse effects. There is a risk for a more severe reaction, however that risk appears to be relatively low. Also, the therapies and management that would be instituted would generally be those for all other allergic reactions.

Dr. Lee recommended that, in order to assess the mechanism for development of angiodema and urticaria, a trial should be conducted in which patients treated with Medisorb Naltrexone are tested for development of antibodies to naltrexone, carboxymethylcellulose, or the combination Medisorb Naltrexone product.

#### *7.1.3.5.7 Reviewer's Conclusion – Allergenic potential of Medisorb Naltrexone*

The data show that patients administered Medisorb Naltrexone were more likely than placebo patients to experience inflammatory-type responses to treatment. Responses included injection site reactions, angioedema, urticaria, eosinophilic pneumonia, and elevations in blood

eosinophils. Three of these responses were serious events, requiring hospitalization with surgical intervention or admission to the intensive care unit. The data suggest that at least half of patients treated with Medisorb Naltrexone will have a localized inflammatory reaction at the injection site, and that patients who have an injection site reaction are likely to have another one upon repeated injection.

These responses are concerning for an allergic or hypersensitivity reaction to Medisorb Naltrexone. However, the data are insufficient to definitively show that this is the underlying mechanism for the adverse effects. Furthermore, the data do not provide information to predict the characteristics of patients who would be at risk for these reactions. The inability to predict these kind of risks makes ascertainment of a risk-benefit balance difficult.

*7.1.3.5.8 BONE MARROW SUPPRESSION*

There was one report of non-serious 'bone marrow suppression' following treatment with Medisorb Naltrexone.

*Subject ALK21003-211-002*

This 43 year old female had a history of alcohol and heroin abuse. Her first dose of Medisorb Naltrexone (380-mg) was on — Blood drawn at the time of the 4th dose ( — showed low WBC and RBC counts. The investigator diagnosed the patient with 'bone marrow suppression' and referred her to a hematologist —— for further evaluation. No further doses of Medisorb Naltrexone were administered. The patient's study laboratory values showed a progressive decrease in WBC, RBC and platelet count:

| Visit | WBC(x10$^3$/uL) | EOS(x10$^3$/uL) | RBC(x10$^6$/uL) | HGB (g/dL) | HCT (%) | PLT(x10$^3$/uL) |
|---|---|---|---|---|---|---|
| **Range** | **3.8-10.7** | **0 – 0.57** | **4.1 – 5.6** | **11.6 – 16.4** | **34 – 48** | **140 - 400** |
| Baseline | 5.13 | 0.27 | 3.8 | 12.0 | 38 | 171 |
| Week 4 | 8.22 | 0.14 | 4.4 | 14.3 | 42 | 117 |
| Week 8 | 3.79 | 0.17 | 4.7 | 14.5 | 44 | 183 |
| Week 12 | 2.44 | 0.11 | 2.9 | 12.8 | 38 | 141 |

She was asymptomatic at evaluation by the hematologist, and physical examination was unremarkable. Laboratory values taken during periodic showed leucopenia, thrombocytopenia, and neutropenia::

| Date | WBC(x10$^3$/uL) | PMNs (%) | Lymphs (%) | Monos (%) | Eos (%) | PLT(x10$^3$/uL) |
|---|---|---|---|---|---|---|
| **Range** | **4 - 11** | **45-85** | **16-50** | **0-10** | **0-6** | **150 - 400** |
| | 2.27 | | | | | 97 |
| | 4.1 | 37 | 36 | 19 | 6 | 171 |
| | 3.5 | 40 | 45 | 11 | 2 | 78 |
| | 6.0 | | | | | 217 |
| | 5.1 | 54 | 31 | 14 | 0 | 230 |

The hematologist's initial impression was transient drug-induced marrow suppression. However, at a follow-up visit with the hematologist, the patient reported continued intermittent drinking which had been occurring even while she was on study medication. Based on this new history, the hematologist's diagnosis was bone marrow suppression secondary to binge drinking.

REVIEWER COMMENT: The overall incidence of bone marrow suppression among all Medisorb Naltrexone-treated participants was 0.1% (1/1049), compared to 0% (0/214) in placebo-treated patients. Based on the patient's history of illness, as well as the lack of reports of bone marrow suppression with oral naltrexone, association of the hematological abnormalities with Medisorb Naltrexone is unlikely.

### 7.1.4 Other Search Strategies

Not applicable.

### 7.1.5 Common Adverse Events

#### 7.1.5.1 Eliciting adverse events data in the development program

All spontaneously reported, elicited, and observed AEs were recorded on the adverse event reporting form. Data collection on AEs began after receipt of the first dose of study drug and continued until at least 30 days after administration of the last dose of study drug. For study ALK21-003, AE data were collected for 6 weeks after the last dose was administered. For studies -001, -002, -004, -005, and -009 AE data were collected for at least 8 weeks after the last dose was given.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using MedDRA 4.1. The appropriateness of the Applicant's coding was assessed by comparing the preferred terms to the verbatim terms recorded by investigators within the CRFs, focusing on the events that led to discontinuation of study participation. The Applicant's coding was found to be reasonably accurate.

#### 7.1.5.3 Incidence of common adverse events

Alkermes used data from its 4-6 month subgroup of trials (studies ALK21-002, ALK21-003, and ALK21-006) to determine the types of common adverse effects associated with Medisorb Naltrexone therapy. Alkermes focused on the common adverse events reported by at least 5% of the patients, and presented the data by Body System (i.e. system organ class) and Preferred Term, in order of descending overall frequency regardless of causality to study drug.

As already discussed, ALK21-002 and -003 were blinded, placebo controlled of trials of Medisorb Naltrexone in patients with alcohol dependence. Whereas ALK21-002 evaluated the efficacy and safety of 400-mg of Medisorb Naltrexone over 4 months, ALK21-003 compared the effects of 190- and 380-mg over 6 months. ALK21-006 was a 1-year open label comparison of Medisorb Naltrexone 380 mg and oral naltrexone 50 mg in patients with alcohol dependence or mixed alcohol-opiate dependence. Only 6-month interim data for this study were available at the

time of data cutoff, therefore this study was included in the 4-6 month subgroup of trials. All studies used the same methods to obtain information on AEs.

Since studies ALK21-002 and -003 were the most similar in dose, duration, choice of control, and population characteristics, I pooled these trials to determine the types and frequency of adverse events. Together, these trials provide a reasonably sized sample (n = 654) to evaluate the effects of Medisorb Naltrexone. I did not include study ALK21-006 in the pool because it was an open label trial of two different types of medication, and due to the possibility that this mixed alcohol-opiate population may have different vulnerabilities to study treatment. Instead, I evaluated the adverse event rates in this trial separately (see Section 7.1.5.6).

### 7.1.5.4 Common adverse event tables

Alkermes found that the most frequently occurring adverse effects associated with Medisorb Naltrexone treatment were gastrointestinal effects: nausea, vomiting, diarrhea, abdominal pain, and decreased appetite. Additional commonly reported adverse events were injection site reactions (tenderness, induration, and pain), fatigue, and dizziness.

I conducted my own analyses to determine the frequency of common adverse events. I first created a subset of the subjects from ALK21-002 and -003 from the ISS adverse event dataset. The events that Alkermes flagged as occurring within the first 6 months of exposure (i.e. within 30 days after the last dose) were identified. AEs were tabulated in order of frequency, by body system (i.e. system organ class) and then by preferred term. In certain instances, preferred terms that were reasonably similar and were appropriately captured by the higher level term (HLT) were combined and the HLT values were included in the table. Events occurring solely or in greater frequency in the placebo group were removed, as well as events unlikely to be related to study treatment (e.g. hernia, dental/gum disorder, cardiac murmur, glucosuria, proteinuria, venipuncture site bruise, facial pain, animal bite/sting, diabetes, macular degeneration, and myocardial infarction). Events occurring in at least 5% of Medisorb Naltrexone patients are shown in Table 7.1.5.4 below. Adverse events occurring in at least 1% of Medisorb naltrexone patients are listed in the Appendix.

I found that gastrointestinal-related AEs were the most often reported type of AE. Per my analysis, more Medisorb Naltrexone patients than placebo patients reported nausea (29% vs. 11%), vomiting (12% vs. 6%), diarrhea (13% vs. 10%), abdominal pain (12% vs. 8%), dry mouth (6% vs. 4%), and flatulence/bloating (2% vs. 0.9%). In general, these AEs were more frequent at the higher doses (380- and 400-mg). Additionally, a greater number of patients in the Medisorb Naltrexone group than in the placebo group experienced a decrease in appetite (11% vs. 3%) and in weight (1.4% vs. 0.5%)

Similar to the Applicant, I found that substantially more patients in the Medisorb Naltrexone group reported asthenia (e.g. fatigue, malaise, lethargy) compared to the placebo patients (20% vs. 12%, respectively). Also, AE reports of injection site reactions were considerably more frequent in the Medisorb Naltrexone group than the placebo group (25% vs. 8%). (See Section 7.1.3.5.1 for a detailed discussion of injection site reactions.) Other effects more numerous in

Medisorb Naltrexone than placebo patients were headache (21% vs. 18%), dizziness (13% vs. 4%), and somnolence/sedation (5% vs. 1%).

Arthralgia, back pain, and muscle cramps also occurred more frequently in the Medisorb Naltrexone group than in the placebo group. The greatest difference between the groups was with respect to muscle cramps (5% vs. 1%), followed by arthralgia (8% vs. 5%) and back pain (6% vs. 5%). Also, more patients treated with Medisorb Naltrexone reported rash 6% vs. 4%) and angioedema/urticaria (2% vs. 0%) (See Sections 7.1.3.5.3 and 7.1.3.5.4).

Treatment with Medisorb Naltrexone appeared to confer a slightly increased risk of psychiatric effects, namely anxiety, insomnia, and depression. Whereas 8% of placebo patients described anxiety conditions, 10% of Medisorb Naltrexone patients reported these events. Similarly, whereas 4% of placebo patients experienced depression and/or suicidal ideation, 6% of Medisorb Naltrexone patients did so. The difference in the risk of insomnia was less considerable between the active and placebo groups (13% and 12%, respectively).

The data showed a slightly greater proportion of patients in the Medisorb Naltrexone group had increases in AST compared to the placebo group (1.6% vs. 0.9%). However, overall, treatment with Medisorb Naltrexone was *not* associated with more frequent increases in liver function tests (AST, ALT, GGT, or bilirubin) compared to placebo (6% vs. 7%).

**Table 7.1.5.4 Reviewer's Analysis of Common Adverse Events (by body system and preferred term/high level group term) in ≥ 5% of patients treated with Medisorb Naltrexone – Studies ALK21-002 and ALK21-003**

| Body system/SOC | Adverse Event/Preferred Term | Placebo | | Medisorb Naltrexone | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N = 214 | | 400-mg N = 25 | | 380 mg N = 205 | | 190 mg N = 210 | | All N = 440 | |
| | | N | % | N | % | N | % | N | % | N | % |
| Gastrointestinal disorders | Nausea | 24 | 11.21 | 8 | 32.00 | 68 | 33.17 | 53 | 25.24 | 129 | 29.32 |
| | Vomiting NOS | 12 | 5.61 | 3 | 12.00 | 28 | 13.66 | 22 | 10.48 | 53 | 12.05 |
| | Diarrhea [1] | 21 | 9.81 | 3 | 12 | 27 | 13.17 | 27 | 12.85 | 57 | 12.95 |
| | Abdominal pain [2] | 17 | 7.95 | 4 | 16 | 23 | 11.22 | 23 | 10.96 | 50 | 11.36 |
| | Dry mouth | 9 | 4.21 | 6 | 24.00 | 10 | 4.88 | 8 | 3.81 | 24 | 5.45 |
| | | | | | | | | | | | |
| Investigations | Abnormal liver function test - Total | 14 | 6.53 | 3 | 12 | 12 | 5.85 | 12 | 5.72 | 27 | 6.15 |
| | | | | | | | | | | | |
| Infections and infestations | Upper respiratory tract infection - Other [3] | 28 | 13.08 | 0 | 0.0 | 27 | 13.17 | 25 | 11.9 | 52 | 11.81 |
| | Pharyngitis [4] | 23 | 10.75 | 0 | 0.0 | 22 | 10.73 | 35 | 16.67 | 57 | 12.95 |
| | | | | | | | | | | | |
| Psychiatric disorders | Insomnia, sleep disorder | 25 | 11.68 | 2 | 8.00 | 29 | 14.15 | 27 | 12.86 | 58 | 13.19 |
| | Anxiety [5] | 17 | 7.94 | 2 | 8.00 | 24 | 11.71 | 16 | 7.62 | 42 | 9.54 |
| | Depression & suicidal ideation combined | 9 | 4.21 | 0 | 0.00 | 17 | 8.29 | 9 | 4.28 | 26 | 5.91 |
| | Depression only | 9 | 4.21 | 0 | 0.00 | 17 | 8.29 | 7 | 3.33 | 24 | 5.45 |
| | Suicidal ideation only | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 2 | 0.95 | 2 | 0.45 |
| | | | | | | | | | | | |
| General disorders and administration site conditions | Injection site reaction - Total | 17 | 7.95 | 5 | 20 | 58 | 28.31 | 46 | 21.92 | 109 | 24.78 |
| | Injection site pain | 12 | 5.61 | 4 | 16.00 | 24 | 11.71 | 19 | 9.05 | 47 | 10.68 |
| | Injection site induration | 4 | 1.87 | 1 | 4.00 | 13 | 6.34 | 7 | 3.33 | 21 | 4.77 |
| | Asthenic conditions [6] | 26 | 12.15 | 3 | 12 | 47 | 22.93 | 40 | 19.05 | 90 | 20.44 |

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

[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: anxiety NEC, anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress

[6] Includes the preferred terms: malaise, fatigue (these two comprise the majority of cases); lethargy, sluggishness

**Table 7.1.5.4 Common Adverse Events (by body system and preferred term/high level group term) in ≥ 5% of patients treated with Medisorb Naltrexone** (contd.)

| Body system/SOC | Adverse Event | Placebo N = 214 | | Medisorb Naltrexone 400-mg N = 25 | | 380 mg N = 205 | | 190 mg N = 210 | | All N = 440 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | N | % |
| Musculoskeletal and connective tissue disorders | Arthralgia,, arthritis, joint stiffness | 11 | 5.14 | 1 | 4 | 24 | 11.71 | 12 | 5.72 | 37 | 8.42 |
| | Back pain, stiffness | 10 | 4.68 | 1 | 4.00 | 12 | 5.86 | 14 | 6.67 | 27 | 6.14 |
| | Muscle cramps [7] | 3 | 1.4 | 0 | 0.0 | 16 | 7.82 | 5 | 2.38 | 21 | 4.77 |
| | | | | | | | | | | | |
| Skin and subcutaneous tissue disorders | Rash [8] | 8 | 3.74 | 3 | 12 | 12 | 5.86 | 10 | 4.76 | 25 | 5.68 |
| | | | | | | | | | | | |
| Nervous system disorders | Headache [9] | 39 | 18.23 | 9 | 36 | 51 | 24.89 | 34 | 16.19 | 94 | 21.36 |
| | Dizziness, syncope | 9 | 4.21 | 4 | 16 | 27 | 13.17 | 27 | 12.85 | 58 | 13.19 |
| | Somnolence, sedation | 2 | 0.93 | 3 | 12 | 8 | 3.9 | 9 | 4.29 | 20 | 4.55 |
| | | | | | | | | | | | |
| Metabolism and nutrition disorders | Anorexia, appetite decreased NOS, appetite disorder NOS | 6 | 2.8 | 5 | 20 | 30 | 14.63 | 13 | 6.19 | 48 | 10.91 |

[7] Includes the preferred terms: muscle cramps, spasms, tightness, twitching, stiffness, rigidity
[8] Includes the preferred terms: rash NOS; rash popular; heat rash
[9] Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches

### 7.1.5.5 Identifying common and drug-related adverse events

See Section 7.1.5.4.

### 7.1.5.6 Additional analyses and explorations

#### *7.1.5.6.1 NAUSEA AND VOMITING*

I used the adverse event data from studies ALK21-002, -003 and -006 (i.e. the studies of 4-6 months' exposure) to explore the time to onset and the duration of nausea and vomiting. The effects of these symptoms on continued study participation were also evaluated.

Among the 1090 treated patients, there were 272 patients (25%) who experienced nausea (n = 240, 22%), vomiting (n = 98, 9%), or retching (n = 2, 0.2%). As already described, more patients treated with Medisorb Naltrexone than with placebo reported nausea (24% vs. 11%) or vomiting (9% vs. 6%). The majority of patients reported symptoms within 1 to 2 weeks of the first dose of study drug. The median duration of symptoms was 1 day, and the mean duration was 6 days (range 0 to 160 days).

A total of 10 patients (0.9%) discontinued treatment due to nausea (n = 10, 0.9%), vomiting (n = 2, 0.2%), and/or retching (n = 1, 0.01%). One patients was treated with Medisorb Naltrexone 190-mg and 9 patients were administered 380-mg. Eight of the 10 patients reported onset of nausea, and 2 of the 10 patients experienced vomiting more than 30 days after the initial dose of study drug. Two of the patients who had nausea described persistent symptoms for 20 and 43 days, respectively.

> REVIEWER COMMENT: Nausea was extremely common among Medisorb Naltrexone patients, and usually occurred early after treatment initiation. Although symptoms generally resolved quickly, some patients had prolonged symptoms and 1% discontinued treatment prematurely because of intolerable symptoms.

#### *7.1.5.6.2 SEDATION/SOMNOLENCE*

Of the 1090 participants in trials ALK21-002, -003, and -006, there were 33 (3.0%) who reported somnolence or sedation following treatment. Although the Medisorb Naltrexone 380-mg group had the highest numerical number of patients experiencing these events (17/576, 2.9%), the 400-mg group had the highest percentage (3/25, 12%). The proportion of patients in the combined 380/400 mg group who reported these symptoms was 3.3% (20/601). Within the 190-mg group 4.3% (9/210,), described sedation or somnolence, followed by the oral naltrexone patients (2/65, 3.1%) Only 0.9% (2/214) of the placebo group had these events. The majority of cases (79%) were considered mild in severity. Only 1 patient had "severe" sedation/somnolence. No patients discontinued due to these symptoms.

Overall, the median time to onset of sedation/somnolence was 7 days (mean = 23 days; range 1-208 days). The oral naltrexone and placebo groups had the shortest median time to onset (~ 3 and 5 days, respectively). Median time to symptom onset in the Medisorb Naltrexone 190-mg, 380-mg, and 400-mg groups was at 6, 12, and 18 days, respectively.

The median duration of sedation/somnolence in all patients was approximately 1 week. The median duration of symptoms was longest for the Medisorb naltrexone 400-mg, oral naltrexone and placebo groups (~ 21 days) compared to the Medisorb Naltrexone 190- and 380-mg groups (4 and 7 days, respectively). However, with respect to the *mean* duration of symptoms, patients in patients treated with Medisorb Naltrexone 400- and 190-mg had the longest mean duration (45 and 37 days, respectively), whereas the Medisorb Naltrexone 380-mg, oral naltrexone and placebo groups had the shortest (19 – 21 days).

REVIEWER COMMENT: The data show that, overall, a low percentage of patients experienced mild sedation/somnolence that did not lead to discontinuation of treatment. The risk of these effects did not appear to be dose related.

### 7.1.6 Less Common Adverse Events

Not applicable.

### 7.1.7 Laboratory Findings

#### 7.1.7.1 Overview of laboratory testing in the development program

During the Phase 2 and 3 trials, laboratory evaluation of safety was conducted using standard hematology, chemistry, and urinalysis tests. Testing for CDT and breath alcohol concentration was done primarily to evaluate treatment efficacy. Studies ALK21-003, ALK21-003EXT and ALK21-010 used a central laboratory, whereas study ALK21-002 used the local hospital/clinic. Any laboratory value considered abnormal and clinically significant by the study investigator was to be reported as an adverse event. All laboratory data were to be presented using descriptive statistics.

The Applicant focused its evaluation of laboratory results on tests of liver function (AST, ALT, GGT, and total bilirubin), as changes in these parameters could be evidence of naltrexone toxicity. Alkermes concluded that the LFT data essentially showed that treatment with Medisorb Naltrexone did not confer a greater risk of increased LFTs than did treatment with placebo. See Section 7.1.3.3.1 for a detailed discussion of the changes in LFTs associated with study treatment.

### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Results from the analyses of the laboratory data are presented for studies of 4-6 month's exposure and > 6 months' exposure. The rationale for pooling these studies has already been provided (see Section 7.1). The laboratory results from the 4-6 month category of studies were selected for analysis because it includes placebo and oral naltrexone groups for comparison.

### 7.1.7.3 Standard analyses and explorations of laboratory data

*7.1.7.3.1 ANALYSES FOCUSED ON MEASURES OF CENTRAL TENDENCY*

The tables below show the mean change in the biochemistry (Table 7.1.7.3.1.a) and hematology (Table 7.1.7.3.1.b) parameters from baseline to the end of the study (Week 24), across the placebo, oral naltrexone, and Medisorb Naltrexone groups.

There was little change from baseline to Week 24 in the electrolyte (sodium and potassium) and renal function (creatinine and BUN) parameters. In addition, analyses of the change in mean values from baseline at each of the monthly visits showed little change, as well as no considerable difference from placebo (data not shown). The placebo group, in comparison to the oral and the Medisorb naltrexone groups, showed the largest increase in mean glucose at Week 24 (i.e. 6 mg/dL). Overall, therefore, there was no consistent drug-related effect on mean sodium, potassium, glucose, total protein, creatinine, and BUN. Chloride was not measured during the clinical trials.

At baseline, the mean CPK values were slightly dissimilar among the groups. At Week 24, the Medisorb Naltrexone 190-mg group showed a mean decrease in CPK, whereas the other groups (including the oral naltrexone group) showed an increase. However, evaluation of the monthly change from baseline in CPK found that the mean values across groups were relatively stable during the treatment period, and not considerably different from placebo (data not shown). Based on these findings, and fact that elevated CPK is known to occur in patients with alcohol abuse, the relatively small increase CPK increase in the 380-mg group at Week 24 was not considered clinically relevant.

**Table 7.1.7.3.1.a: Biochemistry parameters: Mean change from baseline to week 24 – Studies of 4-6 months' exposure**

| | Placebo | Medisorb Naltrexone | | Oral NTX |
|---|---|---|---|---|
| | | 190 mg | 380/400 mg* | |
| **Sodium (mEq/L)** | | | | |
| Baseline | 142.1 | 141.9 | 141.3 | 140.9 |
| Mean change from BL to Wk 24 | -1.1 | -0.7 | -1.2 | -0.2 |
| **Potassium (mEq/L)** | | | | |
| Baseline (mean | 4.36 | 4.32 | 4.34 | 4.35 |
| Mean change from BL to Wk 24 | -0.04 | -0.09 | -0.10 | -0.17 |
| **Creatinine (mg/dL)** | | | | |
| Baseline (mean | 0.86 | 0.86 | 0.85 | 0.84 |
| Mean change from BL to Wk 24 | -0.02 | -0.01 | 0.01 | 0.04 |
| **BUN (mg/dL)** | | | | |
| Baseline (mean) | 14.1 | 13.9 | 13.4 | 14.6 |
| Mean change from BL to Wk 24 | 0.2 | 0.8 | 0.9 | 0.1 |
| **Glucose (mg/dL)** | | | | |
| Baseline (mean) | 97.4 | 101.9 | 96.4 | 96.2 |
| Mean change from BL to Wk 24 | 5.9 | 1.2 | 1.7 | -1.2 |
| **Creatinine phosphokinase (U/L)** | | | | |
| Baseline (mean) | 150.1 | 164.7 | 137.4 | 145.4 |
| Mean change from BL to Wk 24 | 27.7 | -24.2 | 13.4 | 12.8 |
| **Total protein (g/dL)** | | | | |
| Baseline (mean) | 7.46 | 7.46 | 7.49 | 7.50 |
| Mean change from BL to Wk 24 | -0.17 | -0.12 | -0.16 | -0.15 |

* Patients were treated with Medisorb Naltrexone 400-mg in Study ALK21-002 only. Since this was a 4-month (i.e. 16-week) trial, there were no data at 24 weeks for the 400-mg group, and all the data in the combined group were from the 380-mg patients.
(Source: Applicant's Table 1001-1002, supplemental information received 8/8/05)

With respect to the hematology data, there was little change from baseline to Week 24 in the WBC, RBC, hemoglobin, and hematocrit mean values. The Medisorb Naltrexone combined 380/400 group showed a decrease in platelets at Week 24 which appeared to be driven by the 380-mg patients and was consistently observed at each monthly evaluation. Similarly, the decrease in platelets observed in the oral naltrexone group persisted over the duration of treatment (data not shown).

**Table 7.1.7.3.1.b: Hematology parameters: Mean change from baseline to week 24 – Studies of 4-6 months' exposure**

| | Placebo | Medisorb Naltrexone | | Oral NTX |
|---|---|---|---|---|
| | | 190 mg | 380/400 mg* | |
| **WBCs (x 10^3/uL)** | | | | |
| Baseline (mean) | 7.334 | 7.017 | 6.552 | 7.687 |
| Mean change from BL to Wk 24 | -0.138 | -0.003 | -0.482 | -3.48 |
| **RBCs (x 10^3/uL)** | | | | |
| Baseline (mean) | 4.75 | 4.70 | 4.52 | 4.78 |
| Mean change from BL to Wk 24 | 0.02 | 0.05 | 0.02 | 0.05 |
| **Platelets (x 10^3/uL)** | | | | |
| Baseline (mean) | 273.9 | 255.8 | 247.0 | 288.9 |
| Mean change from BL to Wk 24 | -2.6 | -1.6 | -17.8 | -43.1 |
| **Hemoglobin (g/dL)** | | | | |
| Baseline (mean) | 15.01 | 14.92 | 14.92 | 14.87 |
| Mean change from BL to Wk 24 | -0.17 | -0.22 | -0.18 | -0.02 |
| **Hematocrit (%)** | | | | |
| Baseline (mean) | 44.3 | 43.8 | 43.8 | 42.2 |
| Mean change from BL to Wk 24 | -0.7 | -0.4 | -0.1 | 0.4 |

* Patients were treated with Medisorb Naltrexone 400-mg in Study ALK21-002 only. Since this was a 4-month (i.e. 16-week) trial, there were no data at 24 weeks for the 400-mg group, and all the data in the combined group were from the 380-mg patients.
(Source: Applicant's Table 1007-1008, supplemental information received 8/8/05)

REVIEWER COMMENT:
The product label for oral naltrexone does not describe decreased platelets as a consistent adverse effect associated of treatment. However, the label describes one case of idiopathic thrombocytopenic purpura following prior sensitization to oral naltrexone. There were no platelet-related SAEs or AEs reported in the clinical trials with Medisorb Naltrexone.

Overall, the data do not suggest that treatment with Medisorb Naltrexone is associated with sizeable mean changes in hematology or biochemistry parameters, other than platelets.

*7.1.7.3.2 ANALYSES FOCUSED ON OUTLIERS OR SHIFTS FROM NORMAL TO ABNORMAL*

Shifts from the normal to the high range, from baseline to Week 24, are presented in the shift tables that follow. Shift tables from normal to low are also provided for the hematology parameters.

The largest shift in normal to high values was observed for CPK. The Medisorb Naltrexone 380-mg group had a slightly more patients (11%) than placebo (8%) shift from a normal CPK value at baseline to high value at Week 24. The oral naltrexone group had an even higher number (17%) of patients shift from normal to high CPK. A potential reason for this observation, namely alcohol abuse, is described in Section 7.1.7.3.1, above. Another potential explanation is that elevated CPK is an adverse effect of naltrexone treatment.

Otherwise, there were no other significant shifts in biochemistry parameters for the Medisorb Naltrexone and oral naltrexone groups, compared to placebo.

**Table 7.1.7.3.2.a: Shift table for biochemistry parameters – Studies of 4-6 months' exposure**

| Parameter | Placebo BL N = 214 Wk 24 N = 121 | 190-mg BL N = 210 Wk 24 N = 121 | 380-mg BL N = 576 Wk 24 N = 321 | Oral NTX BL N = 65 Wk 24 N = 36 |
|---|---|---|---|---|
| | Shift from normal (BL) to high (Week 24), N (%) | | | |
| CPK | 10 (8) | 6 (5) | 37 (11) | 6 (17) |
| Creatinine | 0 (0) | 1 (1) | 1 (<1) | 1 (3) |
| Glucose | 21 (17) | 12 (10) | 34 (10) | 3 (8) |
| Potassium | 2 (2) | 0 (0) | 3 (1) | 0 (0) |
| Sodium | 2 (2) | 0 (0) | 0 (0) | 1 (3) |
| Total protein | 2 (2) | 2 (2) | 0 (0) | 0 (0) |

(Source: Applicant's Table 1003, supplemental information received 8/8/05)

The tables below show the shifts for the hematology parameters: from normal (baseline) to high (Week 24), and from normal (baseline) to low (week 24). None of the treatment arms showed a significant shift from normal to high for any of the parameters, and there were no considerable differences in the Medisorb Naltrexone and the oral naltrexone groups compared to placebo.

The data regarding shifts from normal to low showed that the oral naltrexone group had the largest shift (6% of patients had a decrease in platelets) compared to the placebo group or either of the two Medisorb Naltrexone groups (2% and 1% of patients, respectively, had platelet decreases). Thus the shift data for the oral naltrexone group are consistent with the observed mean decrease in platelet count. However, while the Medisorb Naltrexone 380-mg group had a mean decrease in platelets, there was no difference from placebo with respect to the proportion of patients who shifted from the normal to the low range.

**Table 7.1.7.3.2.b: Shift table for hematology parameters, normal to high – Studies of 4-6 months' exposure**

| Parameter | Placebo BL N = 214 Wk 24 N = 120 | 190-mg BL N = 210 Wk 24 N = 118 | 380-mg BL N = 576 Wk 24 N = 320 | Oral NTX BL N = 65 Wk 24 N = 36 |
|---|---|---|---|---|
| | Shift from normal (BL) to high (Week 24), N (%) | | | |
| Hematocrit | 1 (1) | 1 (1) | 0 (0) | 0 (0) |
| Hemoglobin | 0 (0) | 0 (0) | 3 (1) | 0 (0) |
| Platelets | 4 (3) | 3 (3) | 8 (2) | 1 (3) |
| RBC | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| WBC | 6 (5) | 5 (4) | 13 (4) | 1 (3) |

(Source: Applicant's Table 1009, supplemental information received 8/8/05)

**Table 7.1.7.3.2.b: Shift table for hematology parameters, normal to low – Studies of 4-6 months' exposure**

| Parameter | Placebo BL N = 214 Wk 24 N = 120 | 190-mg BL N = 210 Wk 24 N = 118 | 380-mg BL N = 576 Wk 24 N = 320 | Oral NTX BL N = 65 Wk 24 N = 36 |
|---|---|---|---|---|
| | Shift from normal (BL) to low (Week 24), N (%) | | | |
| Hematocrit | 2 (2) | 0 (0) | 4 (1) | 1 (3) |
| Hemoglobin | 2 (2) | 0 (0) | 3 (1) | 0 (0) |
| Platelets | 2 (2) | 1 (1) | 4 (1) | 2 (6) |
| RBC | 8 (7) | 6 (5) | 13 (4) | 3 (8) |
| WBC | 2 (2) | 0 (0) | 3 (1) | 2 (6) |

(Source: Applicant's Table 1009, supplemental information received 8/8/05)

*7.1.7.3.3 MARKED OUTLIERS AND DROPOUTS FOR LABORATORY ABNORMALITIES*

Based on the findings from the analyses of mean changes from baseline, and shifts from baseline, only the CPK values were evaluated for extreme outliers.

In the studies of 4-6 months' exposure, there were 10 patients (10/1090, 0.9%) who had extreme (≥ 3 x ULN) CPK values at Week 24: 4 (1.9%) patients in the placebo group, 3 (1.4%) patients in the 190-mg group, and 3 (0.5%) patients in the 380-mg group. These extreme values ranged from 712 to 3231 mg/dL, representing an increase from baseline of 5 to 3158 mg/dL.

Of the 10 patients, 4 had AE reports of elevated CPK, none of which was considered serious. There were 2 patients in the placebo group, and 1 each in the 190-mg and 380-mg Medisorb Naltrexone groups[12]. None of the reports of CPK elevations occurred in the setting of muscle injury, renal disease, infection, increased drinking, or any other potential cause of CPK increases. Thus there is no clear reason for the CPK elevation apart from naltrexone (oral or depot) exposure.

**Table 7.1.7.3.3.a: Subjects with ≥ 3 x ULN CPK value at Week 24 – Studies of 4-6 months' exposure**

| Subject | Baseline CPK (mg/dL)* | Week 24 CPK (mg/dL)* | Change from baseline |
|---|---|---|---|
| ALK21003-209-029 | 277 | 1028 | 751 |
| ALK21003-210-023 | 244 | 1891 | 1647 |
| ALK21003-210-027 | 1857 | 844 | -1013 |
| ALK21003-215-033 | 305 | 848 | 543 |
| ALK21003-216-010 | 707 | 712 | 5 |
| ALK21003-224-005 | 148 | 1289 | 1141 |
| ALK21003-224-017 | 73 | 540 | 467 |
| ALK21003-227-003 | 221 | 1306 | 1085 |
| ALK21006-235-011 | 478 | 1118 | 640 |
| ALK21006-251-016 | 73 | 3231 | 3158 |

12 Subjects ALK21003-210-023 (placebo), ALK21003-210-027 (190-mg), ALK21003-215-033 (placebo), and ALK21006-235-011 (380-mg)

One patient (subject ALK21006-251-016, Medisorb Naltrexone 380-mg)) had progressive and considerable increases in CPK from baseline to Week 24 (see table below). Despite this, he did not have a reported AE of an injection site reaction, abnormal CPK, muscle injury, increased alcohol intake, or abnormal renal function. His only reported AE was an episode of seasonal allergies (hay fever). At the time of the data cut-off he was continuing treatment with Medisorb Naltrexone 380-mg. The CPK value had returned to normal at Week 28.

REVIEWER COMMENT: In the absence of other factors, the cause of this patient's CPK elevations can only be treatment with Medisorb Naltrexone. The reason for the normalization of CPK levels is not clear.

**Table 7.1.7.3.3.b: Subject ALK21006-251-016: Monthly CPK values**

| Visit | Lab value (mg/dL)* | Change from baseline |
|---|---|---|
| Baseline | 73 | - |
| Week 4 | 90 | 17 |
| Week 8 | 120 | 47 |
| Week 12 | 180 | 107 |
| Week 16 | 473 | 400 |
| Week 20 | 132 | 59 |
| Week 24 | 3231 | 3158 |
| Week 28 | 110 | 37 |

* Normal range for CPK: 18 - 198 mg/dL

REVIEWER COMMENT ON CPK VALUES:
The data show that overall, there were sizeable increase in CPK at Week 24 in a few of the study patients, and these values could explain the increases in group mean CPK values that were previously noted (see Section 7.1.7.3.1).

Fewer Medisorb Naltrexone-treated patients than placebo patients experienced these extreme increases in CPK, and no extreme cases were reported in oral naltrexone patients. Also, the CPK increases occurred in the absence of potential causes of CPK elevation, other than intramuscular injection. Thus, the data do not support an association between CPK elevation and treatment with Medisorb Naltrexone.

### 7.1.7.4 Additional analyses and explorations

None.

### 7.1.7.5 Special assessments

See Section 7.1.3.3.

## 7.1.8 Vital Signs

### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured at each of the visits of the Phase 2 and 3 studies. Vital signs included blood pressure (systolic and diastolic), heart rate, body temperature and weight.

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Results from the analyses of the vital signs data are presented for studies of 4-6 month's exposure.

### 7.1.8.3 Standard analyses and explorations of vital signs data

*7.1.8.3.1 ANALYSES FOCUSED ON MEASURES OF CENTRAL TENDENCIES*

The mean vital signs values at baseline, as well as the mean change from baseline to Week 24 are shown in the table that follows. The groups were relatively similar at baseline with respect to mean vital signs and had similar changes (with respect to magnitude and direction) of these values at Week 24. One exception was the change in weight at Week 24: the Medisorb Naltrexone 190-mg group had the largest mean decrease in weight (~2 kg). However, weight loss is a known effect of naltrexone treatment, so this finding is not remarkable.

**Table 7.1.8.3.1.a: Vital signs parameters: Mean change from baseline to week 24 – Studies of 4-6 months' exposure**

| | Placebo | Medisorb Naltrexone | | Oral NTX |
|---|---|---|---|---|
| | | 190 mg | 380/400 mg* | |
| **Systolic BP (mmHg)** | | | | |
| Baseline (mean) | 128.7 | 131.1 | 127.1 | 123.8 |
| Mean change from BL to Wk 24 | -2.8 | -5.6 | -3.6 | -0.5 |
| **Diastolic BP (mmHg)** | | | | |
| Baseline (mean) | 82.3 | 84.2 | 81.5 | 80.2 |
| Mean change from BL to Wk 24 | -1.8 | -4.4 | -1.9 | -2.7 |
| **Heart rate (bpm)** | | | | |
| Baseline (mean) | 76.7 | 77.1 | 76.9 | 75.6 |
| Mean change from BL to Wk 24 | -0.9 | -1.5 | -1.9 | -0.7 |
| **Temperature (° Celsius)** | | | | |
| Baseline (mean) | 36.69 | 36.72 | 36.62 | 36.64 |
| Mean change from BL to Wk 24 | -0.03 | -0.06 | -0.02 | 0.11 |
| **Weight (kg)** | | | | |
| Baseline (mean) | 81.74 | 82.83 | 81.86 | 81.38 |
| Mean change from BL to Wk 24 | -0.30 | -1.78 | -0.62 | -0.79 |

* Patients were treated with Medisorb Naltrexone 400-mg in Study ALK21-002 only. Since this was a 4-month (i.e. 16-week) trial, there were no data at 24 weeks for the 400-mg group, and all the data in the combined group were from the 380-mg patients.
(Source: Applicant's Table 1015-1016, supplemental information received 8/8/05)

### 7.1.9 Electrocardiograms (ECGs)

ECG data were not collected in any of the Phase 2 or Phase 3 trials.

### 7.1.10 Immunogenicity

See Section 3.2.

### 7.1.11 Human Carcinogenicity

Not applicable.

### 7.1.12 Special Safety Studies

#### 7.1.12.1 Safety of Medisorb Naltrexone vs. oral naltrexone in patients with opioid dependence: Studies ALK21-004 and ALK21-006

Naltrexone is an FDA-approved treatment for narcotic addiction. Studies have shown that oral naltrexone produces opioid blockade, blocking the euphoric effects of opioids. One concern regarding the depot (i.e. long lasting) formulation of Medisorb Naltrexone is that patients who abuse opioids and are administered Medisorb Naltrexone may attempt to overcome the blockade with increasing opiate doses. If these increasing doses are used as naltrexone levels decline, death could result.

The Applicant conducted two trials of Medisorb Naltrexone in patients with opioid dependence. The first study, ALK21-004, was a Phase 1 trial evaluating the opiate blockade effects of Medisorb Naltrexone. The other trial, ALK21-006, was a long-term safety study of Medisorb Naltrexone in patients with alcohol and/or opiate dependence.

*7.1.12.1.1 STUDY ALK21-004: OPIOID BLOCKADE EFFECTS OF MEDISORB NALTREXONE*

**Study design:** This was a randomized, double-blind, placebo-controlled, 3-arm, parallel group, single dose trial to evaluate the degree of opioid blockade of Medisorb Naltrexone in non-dependent opioid users.

**Objectives:** The primary objective of this pilot study was to demonstrate blockade of the effects of an opiate agonist (hydromorphone) in opioid-using adults by Medisorb Naltrexone. Opiate blockade was evaluated based on the objective measure of pupil size and on the subject-rated measure, "Do you feel any drug effect?"

The duration and degree of opiate blockade of hydromorphone by a single injection of Medisorb Naltrexone was evaluated as a secondary objective.

**Methodology**
This 4-week trial enrolled non-dependent opioid users and randomized them to one of three dose groups (1:1:1 randomization): Medisorb naltrexone 75, 150, and 300 mg IM. At Study Day 0, eligible subjects were administered a single injection of Medisorb Naltrexone. Seven experimental hydromorphone challenge sessions (to assess the level of opiate blockade) were conducted at Days 7, 14, 21, 28, 42, and 56, with 1 placebo challenge administered at a randomly selected visit.

**Key entry criteria:** Participants were healthy adults aged ≥ 21 years who used opioids non-medically and were not seeking treatment for opioid abuse. They had to demonstrate an adequate response to hydromorphone during the screening challenge sessions. Patients with a major mood, psychotic, or anxiety disorder, as well as those with LFT and CD4 cell count abnormalities were excluded.

**Key endpoints:** The primary efficacy endpoint was the presence of opiate blockade at Day 28, based on pupil diameter and the subject rated measure (Visual Analog Scale (VAS) question), "do you feel any drug effect?" Both pupil size and drug effect were measured at 15-minute intervals during each hydromorphone challenge session, beginning prior to dosing and up to 60 minutes following the final hydromorphone dose.

Secondary endpoints included the assessment of the surmountability of the blockade effect. Safety was assessed in terms of adverse events, laboratory test results, ECG findings, and physical exam findings.

**Key study results**: A total of 27 subjects were enrolled and randomized to 1 of the 3 dose groups. All 27 subjects received a single IM injection of Medisorb Naltrexone at their assigned dose. Six subjects discontinued the study; 1 patient withdrew due to an adverse event (myalgia, mild).

*Efficacy*
The slope of the linear regression line was the principal summary measure used in the statistical evaluation of Medisorb Naltrexone–mediated opiate blockade and of surmountability of that blockade. As expected, prior to Medisorb Naltrexone injections, the hydromorphone drug effect at the baseline challenge session was reflected by decreasing pupil size and median slopes, and these were statistically different from zero for each dose group.

For all groups, slopes for pupil size approached zero in the early hydromorphone challenge sessions following Medisorb Naltrexone dosing, and moved away from zero as the mitigating effects of Medisorb Naltrexone began to wane over time. Subjects in the 300-mg and 150-mg groups demonstrated complete Medisorb Naltrexone–mediated opiate blockade at Day 28. The 75 mg group had a lower degree of blockade with a shorter duration, and only partial blockade was evident at evaluation visits up to Day 14.

With respect to the VAS subjective rating of drug effect, this appeared to be a measure of low sensitivity as compared with the objective measure of pupil size, and the information was less

therefore meaningful. However, For the 150 and 300 mg groups, the data indicated complete blockade at each evaluation visit up to Day 56. For the 75 mg group, the data suggested complete blockade at each evaluation visit up to Day 42. The

For all doses of Medisorb Naltrexone, median slopes for both blockade and surmountability were greater at baseline compared with Day 28, indicating opiate antagonism. The greatest difference was noted for Medisorb Naltrexone 300 mg, indicating a greater degree of opiate antagonism at this dose. The data also indicated that Medisorb Naltrexone is more effective at blocking a 3 mg hydromorphone dose, than at blocking doses of hydromorphone up to 6 mg.

*Safety*
There were no serious or severe AEs during the study. One subject (subject 203-638; 300 mg) had elevated liver function tests reported as an adverse event of mild severity. These were judged to be due to hepatitis C diagnosed during the study. For several other subjects, LFT and other hematology values were outside of normal ranges, but these were attributed to the subjects' underlying medical status and were therefore not reported as adverse events.

No clinically significant changes from baseline in vital signs and physical exam parameters were noted for any study group. Twelve of 27 subjects (44%) experienced at least one injection site reaction (ISR). ISRs included tenderness and induration, and there was 1 instance of slight bruising at the injection site. None of the ISRs were considered to be clinically significant, so none were reported as adverse events. Fewer ISRs were reported in the 300 mg group [3 (30%) versus 4 (44%) in the 75 mg group and 5 (63%) in the 150 mg group].

REVIEWER COMMENT:
The study shows that a single dose of Medisorb Naltrexone will produce significant and long-lasting opiate blockade. Higher doses produce greater and longer effects (as measured by pupil diameter and subjective rating). Medisorb Naltrexone 300-mg had the greatest degree of opiate antagonism, compared to 150- and 75-mg. Medisorb Naltrexone blocks the effects of lower doses of opiates (i.e. hydromorphone) better than the effects of higher opiate doses.

Based on these data, it is reasonable to conclude that Medisorb Naltrexone 380-mg will also produce clinically significant opiate blockade for at least 28 days after drug administration. This has implications for patient treatment because patients treated with opioids for other conditions may require higher doses to achieve the same effect. Additionally, patients who abuse opioids and are administered Medisorb Naltrexone may attempt to overcome the blockade with increasing opiate doses. If these higher doses are used as naltrexone levels and opiate blockade decrease, overdose and death could result.

*7.1.12.1.2 STUDY ALK21-006: LONG-TERM SAFETY OF MEDISORB NALTREXONE IN PATIENTS WITH ALCOHOL AND/OR OPIOID DEPENDENCE*

**Study design:** This was a 1-year, randomized, open-label, 2-arm, parallel group trial in patients with alcohol and/or opiate abuse.

**Objectives:** The primary objective was to evaluate the long-term safety of Medisorb Naltrexone 380-mg in adults with alcohol and/or opiate dependence.

**Methodology:** Eligible subjects were randomized (6:1) to either Medisorb Naltrexone (380-mg IM q 28 days) or oral naltrexone (50-mg PO daily). Randomization was stratified by previous history of alcohol dependence alone versus opiate dependence or mixed substance abuse. All subjects received standardized psychosocial support (BRENDA) at each study visit. Safety evaluations included physical examinations, ECGs, laboratory measures (hematology, blood chemistry, and urinalysis), plasma concentrations of naltrexone and 6β-naltrexol, and assessments of injection sites and adverse events.

**Key entry criteria:** Enrollees were healthy treatment-seeking adults with alcohol and/or opiate dependence. Subjects with active hepatitis or evidence of hepatic failure were excluded. Patients with a diagnosis of hepatitis C were not specifically excluded.

**Key endpoints**:
The incidence of AEs by treatment group was presented, as well as descriptive statistics summarizing changes in vital signs during dosing and changes in laboratory parameters. Time to discontinuation of study treatment was summarized using Kaplan Meier survival curves.

**Key study results**: A total of 436 subjects were randomized and received study drug (Medisorb Naltrexone, n = 373; oral naltrexone, n = 63). There were 315 patients who had a diagnosis of alcohol dependence and 121 had a diagnosis of opiate dependence or a mixed dependence. Of these latter 121, 101 patients were randomized to Medisorb Naltrexone 380 mg, and 20 were randomized to oral naltrexone. As of the August 31 2004 data cutoff date, enrollment for the study was complete. Altogether, 272 subjects had completed their 24 week visit (Medisorb Naltrexone, n = 232; oral naltrexone: n = 40). The 232 Medisorb Naltrexone subjects had all received at least 6 doses. Three subjects had completed the study, 217 were ongoing, and 216 had discontinued.

*Interim safety results*
Because the study is ongoing, only interim data are available for assessments made during the 24-week study period up until the time of subjects' seventh administration of study drug. As of the cutoff date, 371 subjects received Medisorb Naltrexone and 65 subjects received oral naltrexone.

Up to the Week-24 dosing, a total of 376 subjects (86.2%) experienced at least one AE: 87.3% (324 subjects) of the Medisorb Naltrexone group vs. 80.0% (52 subjects) of the oral naltrexone group. The most commonly observed AEs (in order of frequency) were nausea, headache NOS,

insomnia, and nasopharyngitis. Reported incidence for Medisorb Naltrexone compared favorably to that for oral naltrexone (18.6% vs. 27.7%). The side effect profile for Medisorb Naltrexone compared favorably with that of oral naltrexone for other gastrointestinal AEs considered treatment-limiting for subjects being treated with oral naltrexone: vomiting and abdominal pain.

There were 8 patients who reported 9 adverse events of non-study drug overdose (Medisorb Naltrexone, n = 8; oral naltrexone, n =1). Three of the events heroin overdoses (Medisorb Naltrexone, n = 2; oral naltrexone, n = 1). The remaining 6 cases involved non opioids. Of the 3 cases of heroin overdose, all of the patients[13] experienced their overdose in the context of resumption of heroin use, with or without evidence of suicidal ideation (See Sections 7.1.2 and 7.1.16). In all cases, the overdose occurred more than 30 days after the last administration of study medication (75 days and 60 days for the subjects receiving Medisorb Naltrexone, and 53 days for the subject receiving oral naltrexone). All subjects recovered.

With respect to liver function tests, overall there were no considerable differences between groups or changes from baseline within groups over the duration of the study. Additionally, there were no overall significant changes in serum chemistry parameters. Results for each parameter were similar for each group.

REVIEWER COMMENT:
Interim (6-month) data from this 1-year trial in patients with alcohol and/or opiate dependence show that the most common adverse effects of treatment with Medisorb Naltrexone are those related to the active moiety (naltrexone), and are primarily gastrointestinal. The data do not demonstrate a clinically significant effect on liver function tests. Among patients with concomitant opiate abuse, overdosage with an opioid occurred in 2.5% (3/121) of patients, with a slightly greater frequency in the oral naltrexone (1.5%) than in the Medisorb Naltrexone group (0.5%).

Given that these are interim data only, conclusive statements cannot be made about the safety of long-term administration of Medisorb Naltrexone to patients with alcohol and/or opiate dependence. Nevertheless, the data suggest that long-term administration of 380-mg is reasonably safe with respect to risk of LFT changes and expected gastrointestinal effects. However, due to the long-term duration of opiate blockade ($\geq$ 30 days), there is a risk of opioid overdose in patients who abuse opioids.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Oral naltrexone does not induce tolerance, nor does its withdrawal induce a withdrawal syndrome.

Although no specific data were collected on withdrawal and rebound after discontinuation of Medisorb naltrexone, there were no reported adverse events of withdrawal, rebound, or abuse.

13 Subjects ALK21-006-231, Medisorb Naltrexone; ALK21-006-235, oral naltrexone; ALK21-006-233-005.

### 7.1.14 Human Reproduction and Pregnancy Data

Based on pre-clinical findings, oral naltrexone was categorized as a Pregnancy Category C drug. The product label states that oral naltrexone should be used in pregnancy only when the potential benefit justifies the potential risks to the fetus.

Controlled studies of naltrexone have not been performed in pregnant women. Alkermes reviewed the published literature for information of the effects of naltrexone during pregnancy. There has been experience with naltrexone in only small numbers (i.e. < 50) of pregnant opiate-dependent patients for either rapid opiate detoxification or as a maintenance pharmacotherapy to discourage opiate use. Naltrexone maintenance therapy has been administered orally, or in relapsing opiate abusers, by subcutaneous implants releasing therapeutic levels of the drug for periods estimated at up to 8 months. Alkermes considered the obstetrical and neonatal outcomes to be unremarkable when naltrexone was administered either orally or by subcutaneous implantation.

No human studies have been conducted to determine if naltrexone is distributed into milk. However, naltrexone and its metabolite 6β-naltrexol were detected in the milk of one lactating subject with opiate dependence who was receiving oral naltrexone. It was estimated that naltrexone exposure in the breastfeeding infant of the subject amounted to 0.03% of the maternal dose.

Although the Medisorb Naltrexone trials excluded women of childbearing potential who did not use appropriate contraception, 13 pregnancies were reported: (4 during ALK21-003, 2 during ALK21-003-EXT, and 7 during ALK21-006), all among women treated with Medisorb Naltrexone 380-mg. Durations of exposure to study drug ranged from 1 day to 340 days. Three women experienced missed or spontaneous abortions (duration of exposure, 36, 55, and 153 days). Five women elected to terminate their pregnancy. One woman was lost to follow-up, and the outcome of the pregnancy is unknown. Of the 4 pregnancies ending in live births, all babies were healthy, and there were no reports of congenital anomalies.

> REVIEWER COMMENT: Previous non-clinical data suggest that human *in utero* exposure to naltrexone may have adverse consequences. Although encouraging, the Applicant's limited data regarding human exposure to naltrexone (oral or Medisorb Naltrexone) during pregnancy are

### 7.1.15 Assessment of Effect on Growth

Not applicable.

### 7.1.16 Overdose Experience

Naltrexone is a pure opioid antagonist. It is not known to lead to physical or psychological dependence, nor is tolerance to the opioid antagonist effect known to occur.

There is minimal information regarding the effects of naltrexone overdose. In a clinical study of oral naltrexone in patients with obesity, subjects were given doses of 300 mg/day (6 times the recommended dose for alcohol and narcotic addiction). Elevated transaminases were noted (up to 18 times the baseline values) after 3 – 8 weeks of treatment.

Doses of up to 784 mg IM of Medisorb Naltrexone were administered to healthy subjects (n = 5). There were no serious or severe adverse events. The most common AEs were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. Significant increases in LFTs were not noted. The maximum doses administered to patients with alcohol or opiate dependence were 400-mg (x 4 months) and 380-mg (≥ 6 months), respectively. Effects of administration of these doses have already been described.

There is no information regarding overdosage with Medisorb Naltrexone in patients with hepatic or renal impairment.

Medisorb Naltrexone is to be administered intramuscularly by a physician or other medical professional. It will not be provided directly to patients. This will reduce the likelihood that a patient will overdose on Medisorb Naltrexone.

#### 7.1.17 Postmarketing Experience

Medisorb Naltrexone is not marketed in any other country. Post-marketing experience with oral naltrexone is described elsewhere in this review.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Section 7.1 describes the trials, summary reports, and databases that were used to evaluate the safety of Medisorb Naltrexone.

##### 7.2.1.1 Study type and design/patient enumeration

See Section 4.2 for a table enumerating all subjects and patients across the development program.

##### 7.2.1.2 Demographics

A total of 1232 study participants are included in the application. The majority of patients were white, (967, 78.5%) and male (822, 66.7%). The mean age of patients in the Phase 2-3 studies

was approximately 44 years. A total of 30 subjects (2.4%) in the clinical program were 65 years or older at the start of treatment. No pediatric (<18 years of age) subjects have been studied.

Of the1232 participants in all trials, 969 (78.7%) were alcohol but not opiate dependent, 121 (9.8%) were opiate dependent or had mixed alcohol and opiate dependency, 27 (2.2%) were non-dependent opiate users, 12 (1.0%) had hepatic impairment but were not substance dependent or users, and 103 (8.4%) were healthy subjects.

Tables of the demographic information for the Phase 1 and Phase 2-3 studies are located in the Appendix.

### 7.2.1.3 Extent of exposure (dose/duration)

The Agency advised the Applicant that for this chronically administered drug, data would be required illustrating the safety experience in at least 300 patients treated for 6 months, and at least 100 patients treated for one year. The Applicant was further advised that the safety database should include a sufficient number of subjects with the typical co-morbidities of the target population.

Table 7.2.1.3 (next page) summarizes the dose and duration experience, by clinical trial, with Medisorb Naltrexone. There were 571 patients who were administered at least 6 Medisorb Naltrexone injections (i.e. had at least 6 months of exposure), 394 of whom were treated with the desired to-be-marketed dose, 380-mg. A total of 225 patients had at least 12 injections (i.e. at least 1 year of exposure), 127 of who were administered 380-mg. Therefore, in terms of total number of persons and administered dose, there has been adequate drug exposure.

Studies ALK21-004 and ALK21-006 enrolled patients with a history of opioid abuse. There were 27 non-dependent opiate abusing subjects in ALK21-004, all of whom received a single dose of Medisorb Naltrexone (75-mg, n = 9; 150-mg, n = 8; 300-mg, n = 10). ALK21-006 enrolled 121 patients with alcohol and/or opiate dependence, and 101 were randomized to Medisorb Naltrexone 380 mg. By the time of the data cutoff date, 66 of the 101 patients had been administered at least 6 injections (≥ 6 months' exposure), and 11 had had at least 12 injections (≥ 12 months' exposure).

Demographic data from the Phase 2 and 3 trials of 4-6 months' exposure (ALK21-002, -003, and -006) showed that 803 patients were randomized to treatment with Medisorb Naltrexone. Among these patients, the most commonly reported baseline medical conditions were: depression (47%), hypertension (26%), insomnia (22%), anxiety (22%), headache (17%), seasonal allergies (12%), drug abuse (~11%), and back pain (10%). Approximately 3% had a history of LFT elevations. Three patients (0.4%) had a history of alcoholic hepatitis, and 29 (3.6%) had viral hepatitis.

In general, the data suggest that the study participants' medical histories were consistent with that of the target population. However, since the studies' entry criteria prohibited enrollment of patients with significant medical conditions including considerable cardiac, renal, and hepatic

renal abnormalities, the subjects may not fully reflect severity of diseases commonly noted in alcoholism.



APPEARS THIS WAY
ON ORIGINAL

**Table 7.2.1.3: Cumulative exposure to Medisorb Naltrexone**

**Table 2.5: Overall Cumulative Exposure of Vivitrex Suspension**

| | at least 1 Injections | | at least 3 Injections | | at least 6 Injections | | at least 12 Injections | | at least 18 Injections | | at least 24 Injections | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Identifier | <380 mg | >=380 mg | <380 mg | >=380 mg | <380 mg | >=380 mg | <380 mg | >=380 mg | <380 mg | >=380 mg | <380 mg | >=380 mg |
| ALK21-001[1] | 20 | 15 | | | | | | | | | | |
| ALK21-002 | | 25 | | 21 | | | | | | | | |
| ALK21-003 | 210 | 205 | 169 | 161 | 137 | 130 | | | | | | |
| ALK21-003 EXT | 55[2] | 60[2] | 48[2] | 48[2] | 40[2] | 32[2] | 98 | 91 | 50 | 46 | | |
| ALK21-010 | | | | | | | | | 6 | 13 | 27 | 22 |
| ALK21-004 | 27 | | | | | | | | | | | |
| ALK21-005 | 12 | 24 | | 11 | | | | | | | | |
| ALK21-006 | | 371 | | 300 | | 232 | | 36 | | | | |
| ALK21-009 | 25 | | | | | | | | | | | |
| Subtotal | 349 | 700 | 217 | 541 | 177 | 394 | 98 | 127 | 56 | 59 | 27 | 22 |
| Grand Total | 1049 | | 758 | | 571 | | 225 | | 115 | | 49 | |

SOURCE: Appendix Table 2.7.4.1
1 Fifteen Subjects in ALK21-001 received Vivitrex by SC injection. All other Vivitrex administrations were IM.
2 These subjects received placebo during the ALK21-003 study and were crossed over to Vivitrex suspension in ALK21-003-EXT

(Source: Applicant's Table 2.5, Summary of Clinical Safety, P. 39)

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used to evaluate the safety of Medisorb Naltrexone.

#### 7.2.2.1 Other studies

Not applicable.

#### 7.2.2.2 Postmarketing experience

There is no post marketing experience with Medisorb Naltrexone.

#### 7.2.2.3 Literature

To support its claims regarding the safety of naltrexone, the Applicant relied upon published non-clinical and clinical studies using naltrexone, administered either orally or subcutaneously.

As stated in Section 7.1, the Applicant's summary of the safety of oral naltrexone in alcoholism is passed on 22 published trials (20 randomized, 2 open-label) in patients with alcohol dependence. The studies were conducted between 1992 and 2004. Alkermes focused its review of the studies on the observed common adverse effects of naltrexone.

The literature search appears adequate, and to contain the information necessary to evaluate the previous experience with naltrexone.

### 7.2.3 Adequacy of Overall Clinical Experience

See Section 7.2.1 for a discussion of the adequacy of the extent and duration of exposure to treatment with Medisorb Naltrexone.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Section 3.2.

### 7.2.5 Adequacy of Routine Clinical Testing

Safety testing in the clinical studies included vital signs, physical examination (including examination of the injection sites), general hematology and chemistry testing (including liver function tests), urinalysis, and questioning about adverse events (using open-ended questioning). Safety was assessed at the monthly clinical visits, as well as during the periodic telephone contacts. The safety testing was adequate.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Information about the metabolism and excretion of orally administered naltrexone is already known. To evaluate the pharmacokinetics of Medisorb Naltrexone (i.e. injected naltrexone), the Applicant conducted two trials in healthy subjects and one trial in patients with mild-moderate hepatic impairment. Finally, a population PK analysis was conducted using information from the studies in patients with alcohol and/or opiate dependence. This testing was considered adequate. (See Section 5 for details.)

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The primary effects of concern with Medisorb Naltrexone treatment included hepatotoxicity and injection site reactions. At each of the monthly clinic visits, liver function tests were measured and injection sites were examined. This type and frequency of testing was adequate.

Although not intended as a treatment for narcotic addiction, the effects of Medisorb Naltrexone were studied in patients with alcohol and/or opiate dependence (Study ALK21-004). This is because there is the potential for "off label" treatment of patients with opioid dependence. In this population, Medisorb Naltrexone could precipitate opioid withdrawal or lead to overdose. Despite this, Study ALK21-004 did not specifically require evaluation of these events. Instead, opioid withdrawal and overdose were captured only as patient-reported adverse events. This was adequate.

### 7.2.8 Assessment of Quality and Completeness of Data

The original NDA submission, together with additional information provided upon the Division's request over the course of the NDA review, provided sufficient data to conduct the safety review. Data regarding patient exposure, disposition, and adverse events were the focus of the review and, overall, were complete enough to make a determination regarding the safety of the product at the proposed treatment dose.

### 7.2.9 Additional Submissions, Including Safety Update

**Safety Update Report:**

The original NDA submission contained final safety information for all studies except for three extension studies: ALK21-006, ALK21-006-EXT, and ALK21-010. Although study ALK21-006 was completed, at the time of the data cut-off (August 31 2004) only interim safety data were available, primarily for patients who had had up to 6 months' of drug exposure. At data cut-off and NDA submission, enrollment in ALK21-010 was ongoing and so interim results were provided for that trial as well. At NDA data cut-off date, enrollment for study ALK21-006-EXT had just begun.

The 120-day Safety Update contains new safety data from the completed ALK21-006, as well as immediately available data for the ongoing ALK21-006-EXT and ALK21-010 extension studies (up until March 31 2005). Thus, all of the data is from patients with greater than 6 months of treatment exposure. The Safety Update information, collected between August 31 2004 and March 31 2005, will be referred to as the "SUR (Safety Update Report) data."

*Subject population*
As of March 31 2005, there have been 1,232 subjects enrolled in clinical trials of Medisorb Naltrexone. No new subjects were enrolled during the SUR period. Study ALK21-006 had completed enrollment at the time of the original NDA submission, and patients who subsequently enrolled in ALK21-006-EXT were simply a subset of the ALK21-006 population. Similarly, subjects enrolled in ALK21-010 were a subset of those previously enrolled in the efficacy study ALK21-003 and its extension study, ALK21-003EXT.

A total of 574 subjects (332 from ALK21-003 and 242 from ALK21-006) continued on treatment for more than 6 months, representing 54% of all subjects who enrolled in these primary studies.

After the original NDA data cut-off date (August 31 2004), there were 290 patients active in clinical trials: 45 treated with Medisorb Naltrexone 190-mg, 231 treated with Medisorb Naltrexone 380-mg, and 30 patients treated with oral naltrexone.

*Exposure*
During the SUR period there were 16 new patient exposures to Medisorb Naltrexone. These 16 patients were treated with oral naltrexone during study ALK21-006, and then were administered Medisorb Naltrexone 380-mg during the extension study, ALK21-006-EXT. Consequently, since March 31 2005, a total of 1065 subjects (1049 in the original NDA + 16 new exposures) have been given at least one dose of Medisorb Naltrexone: 84 healthy subjects, 12 with hepatic impairment who were not substance dependent, 27 non-dependent opioid users, 104 with alcohol and/or opiate dependence, and 838 patients with alcohol dependence.

The total exposure in patients with a history of alcohol and/or opiate use, by number of doses received, is shown in Table 7.2.9. Among these patients, 942 have received at least one dose of Medisorb Naltrexone. A total of 400 patients have be been treated with the proposed to-be-marketed dose (380-mg) for at least 6 months, and 229 have been treated with this dose for at least 1 year.

The maximum duration of exposure for subjects is 38 months (n = 3, 190-mg). One patient has been treated with 380-mg for a maximum of 37 months.

**Table 7.2.9.a: Summary of Medisorb Naltrexone exposure in patients with a history of alcohol and/or opiate use**

| | At Least 1 Injection | | At Least 6 Injections | | At Least 12 Injections | | At Least 18 Injections | | At Least 24 Injections | | At Least 30 Injections | | At Least 36 Injections | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | 190mg | 380mg | 190mg | 380mg | 190mg | 380mg | 190mg | 380mg | 190mg | 380mg | 190mg | 380mg | 190mg | 380mg |
| ALK21-002* | | 25 | | | | | | | | | | | | |
| ALK21-003 | 210 | 205 | 137 | 130 | | | | | | | | | | |
| ALK21-003EXT[1] | 55 | 60 | 40 | 32 | 98 | 91 | 50 | 46 | | | | | | |
| ALK21-010[2] | | | | | | | 12 | 17 | 39 | 47 | 23 | 19 | 5 | 4 |
| ALK21-006 | | 371 | | 232 | | 136 | | | | | | | | |
| ALK21-006EXT[3] | | 16 | | 6 | | | | 25 | | | | | | |
| Subtotal | 265 | 677 | 177 | 400 | 98 | 229 | 62 | 88 | 39 | 47 | 23 | 19 | 5 | 4 |
| Grand Total | 942 | | 577 | | 327 | | 150 | | 86 | | 42 | | 9 | |

SOURCE: J:\BDM\NALTREXONE\NDA120D\PROG\TABLES\DEV\ISS_EXPOSURE.SAS 30JUN2005@10:01
* Vivitrex dose for 25 subjects in ALK21-002 was 400mg.
[1] ALK21-003EXT is the extension of ALK21-003.
[2] ALK21-010 is the extension of ALK21-003EXT.
[3] ALK21-006EXT is the extension of ALK21-006.
Note: Table indicates the number of subjects who achieved dosing criterion stated in the column heading first time with the cumulative number of Vivitrex doses received.

*Dropouts due to adverse events*
During the SUR period, 10 patients (3.4%) discontinued treatment because of an AE. The most frequent AEs leading to early study withdrawal were injection site reactions (1%, 3/290) and suicide-related AEs (0.7%, 2/290). The other types of AEs, including abnormal liver function tests and nausea, each resulted in study discontinuation for only 1 patient. (See the Appendix for a listing of the AEs leading to discontinuation.)

The narratives for the patients who discontinued treatment early due to an AE were reviewed. In addition to the injection site reactions, the following AEs were considered to be drug-related: nausea, generalized rash, and elevated liver enzymes (n = 1, each).[14]

*Deaths*
One patient (subject ALK21-010-214-008) died during the SUR period. The patient was a 52 year old male with a history of alcohol dependence and depression. He committed suicide 22 days after his 33rd dose of Medisorb Naltrexone 190-mg. Given the patient's pre-existing risk factors for suicide, as well as the long duration of treatment before the suicide occurred, the patient's death is unlikely to be related to study treatment.

Altogether, there have been 5 deaths in patients enrolled in Medisorb Naltrexone trials. Four of the deaths were described in the original NDA submission. All of the deaths were not likely related to study medication.

*Serious Adverse Events*
During the SUR period, 25 subjects (8.6%, 25/290) experienced an SAE. The frequency of SAEs was greatest in the oral naltrexone group (10%, 3/30), followed by the Medisorb Naltrexone 380-mg group (8%, 19/231), and then the Medisorb Naltrexone 190-mg group (7%, 3/45).

"Alcoholism" (i.e. lack of treatment efficacy) was the most frequently reported SAE (n = 4), highest in the oral naltrexone patients (7%) than the 190-mg or 380-mg patients (0% and 0.8%, respectively). Suicide-related AEs (suicidal ideation, suicide attempt, completed suicide) were as frequent (n = 4), with 3 (1.3%) patients in the 380-mg group and 1 (2.2%) patient in the 190-mg group reporting this SAE. Otherwise, SAEs varied in type and occurred in relatively low frequencies across groups. The SUR SAE profile was not considerably different from that noted in the original NDA.

The patient narratives for the following SAEs were reviewed for a possible association to study treatment: pneumonia, cellulitis, and suicide-related AEs. None of the narratives suggested a relationship between the SAE and study drug.

A table of the SAEs experienced during the SUR period is located in the Appendix.

14 Subject ALK21006-234-001: rash; Subject ALK21006-241-024: elevated liver enzymes; Subject ALK21-006-EXT-241-004: nausea;

*Common adverse events*
Altogether, 271 patients (71%) continuing with treatment during the SUR period reported at least one AE. The Medisorb Naltrexone 190-mg had the highest proportion of AEs (80%, 36/45)), followed by the 380-mg group had (70%, 161/231), and the oral naltrexone group had (63%, 10/16) (see Appendix Table 10.11.4).

Infections of the upper respiratory tract (URIs, sinusitis, nasopharyngitis) were the most commonly reported AEs (21% of patients). Musculoskeletal and psychiatric abnormalities were prevalent. Specifically described were arthralgia (6%) and back pain (4%), as well as depression (6%), anxiety (4%), and insomnia (4%).

Overall, the profile of common AEs during the SUR period is similar to that noted in the original NDA data, except that gastrointestinal AEs (e.g. nausea) were not as frequent.

*Other significant adverse events*
Based on the original NDA data, hepatotoxicity, injection tolerability, opiate abuse/overdose, non-infectious pneumonia, and eosinophilia were identified as important safety concerns of study treatment.

Hepatotoxicity
There was one report of hepatitis C during the safety update period, with no other AEs of hepatitis reported. Two subjects had AEs of "liver function tests NOS abnormal." ALT and AST have not shown a trend towards increased concentrations with continued Medisorb Naltrexone exposure.

Injection tolerability
Over the SUR period, 63 subjects (23%) experienced an ISR, representing 3% of all injections administered over the same time. Induration and tenderness comprised the majority of reported ISRs; each of the other categories (pain, pruritus, ecchymosis, and other) accounted for less than 1% of ISRs. (See the Appendix for a table listing the injection site reactions.)

Opiate abuse/overdose
No episodes of opiate overdose were reported in the safety update period.

Non-infectious pneumonia
No AEs of nonbacterial pneumonia were reported in the safety update period.

Eosinophilia
There were no AE's of eosinophilia reported in the safety update period. Alkermes did not find a trend towards increased eosinophil counts with continuing dosing.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

### 7.3.1 Selected drug-related adverse events

Overall, patients treated with Medisorb Naltrexone were more likely to report reactions that were consistent with an allergic or hypersensitivity-like reaction: inflammatory injection site reactions, urticaria, angioedema, eosinophilic pneumonia, and elevated blood eosinophils. Some of these reactions were serious and required medical intervention (e.g. tissue necrosis following injection and requiring surgical debridement, hospitalization for pneumonia). Of all the allergic-type events, injection site reactions were the most frequent. They were also consistently shown to be related to administration of Medisorb Naltrexone, as well as to be treatment limiting.

Refer to Section 7.1.3.5 for a complete discussion of these events.

### 7.3.2 Data limitations

None.

## 7.4 General Methodology

Methodology for analysis of efficacy is discussed in Section 6.

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

The rationale for pooling data for the safety analyses is discussed in Section 7.1

#### 7.4.1.2 Combining data

See Section 7.1.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

The relationship between drug dose and adverse events, if present, is discussed individually for the observed AEs.

#### 7.4.2.2 Explorations for time dependency for adverse findings

See Section 7.1.5.6.

#### 7.4.2.3 Explorations for drug-demographic interactions

There were no drug-demographic interactions with regards to safety.

#### 7.4.2.4 Explorations for drug-disease interactions

See Section 7.1.12

#### 7.4.2.5 Explorations for drug-drug interactions

See Section 5.

### 7.4.3 Causality Determination

Three major criteria for establishing causality of a factor are a strong association between the factor and the outcome, a consistent relationship between the factor and outcome, and a biologically plausible basis for the relationship.

Numerous drugs are known to cause allergic reactions including urticaria, eosinophilic pneumonia and elevated blood eosinophils. Across the various trials, the data showed that there is a consistently greater risk of these kinds of allergic-type responses in Medisorb Naltrexone patients than in placebo-treated patients. Although oral naltrexone has not historically been associated with allergic adverse events, there have been reports of eosinophilia following oral treatment. Also, in Study ALK21-006 patients treated with oral naltrexone showed similar increases in peripheral eosinophils as did patients given Medisorb Naltrexone 380 mg. This dose of Medisorb Naltrexone had been associated with a larger mean increase in eosinophils than placebo treatment (Study ALK21-003).

However, review of these same data by Dr. Charlese Lee found that the evidence is not overwhelming for a causal relationship between Medisorb Naltrexone and hypersensitivity reactions. Thus, the data are merely suggestive of a relationship and causality remains to be determined (see Section 7.1.3.5.6 for details).

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

In the efficacy and extension trials, Medisorb Naltrexone was administered every 28 (+/- 3) days. The Applicant proposes a "monthly" dosing regimen, primarily for ease of prescription and administration. The proposal is based on evidence of a similar degree of opiate blockade at 30-31 days as at 28 days. Thus, the Applicant believes, the efficacy of the Medisorb Naltrexone would not change whether the drug is given every 28 days, or every month.

Alkermes proposes monthly treatment with 380-mg only. Based on its own analyses, the company found no evidence of efficacy of the 190-mg dose. The safety data suggest that the higher dose is associated with more adverse events, including injection site reactions and gastrointestinal effects.

I agree that dosing with Medisorb Naltrexone on a monthly basis yields a similar pharmacologic profile as dosing every 28 days. Dose modification does not appear to be indicated for patients with hepatic impairment. However, due to the risk of bleeding, intramuscular injections should not be given to patients with severe renal impairment.

Per the Agency's analysis, the 380-mg dose does not clearly show any clinically meaningful efficacy. Efficacy is suggested in patients who are abstinent from drinking prior to initiation of treatment. Should the Applicant conduct another appropriate trial and show efficacy using the currently recommended endpoint, a dosing regimen of 380mg IM every month would be acceptable.

## 8.2 Drug-Drug Interactions

Drug interaction studies specifically with Medisorb Naltrexone have not been performed. The Applicant's *in vitro* drug metabolism studies using fluorogenic substrates suggested that naltrexone does not inhibit cytochrome P450 (CYP) enzymes at clinically relevant concentrations. However, the preferred studies using conventional substrates were not conducted, therefore the demonstration of lack of CYP inhibition has not been definitively shown.

Naltrexone blocks the effects of opioids. Therefore, dosage adjustment may be necessary in patients treated with opioids for pain. Also, patients with a history of opioid abuse must be cautioned about the risk of overdose should they attempt to overcome the blockade effect with high doses of opioids.

Medisorb Naltrexone treatment is associated with neuropsychiatry effects such as sedation, dizziness, anxiety, and insomnia. Caution should be employed when co-administering drugs that have similar effects.

## 8.3 Special Populations

*Hepatic impairment*
Naltrexone undergoes extensive hepatic metabolism. Safety studies of Medisorb Naltrexone were conducted only in patients with mild-moderate hepatic impairment and their matched controls (Study ALK21-009). Patients with severe hepatic impairment were excluded due to the risk of bleeding following intramuscular injection.

In study ALK21-009, patients were administered a single IM dose of Medisorb Naltrexone 190-mg. Pharmacokinetic analysis showed that the average exposure for naltrexone and 6-beta-naltrexone, based on $AUC_{0-\infty}$, was comparable between healthy subjects and subjects with mild-moderate hepatic impairment. In contrast, previous reports for oral naltrexone showed that naltrexone exposure was significantly increased in subjects with hepatic impairment compared with healthy subjects. This was due to decreased first pass metabolism of naltrexone in the hepatic impairment patients, which resulted in increased naltrexone bioavailability.

Based on these findings, it should not be necessary to adjust the dose of Medisorb Naltrexone in subjects with mild or moderate hepatic impairment.

*Renal impairment*
Naltrexone and its metabolized are primarily excreted in the urine. The product label for oral naltrexone does not require dosage adjustment for renally impaired patients. Studies of Medisorb Naltrexone in patients with renal impairment were not performed. Instead, the effects of renal impairment on the pharmacokinetics of Medisorb Naltrexone were evaluated using population PK data from multiple Phase I studies (see Section 5).

*Older populations*
Studies of Medisorb Naltrexone were not specifically conducted in elderly patients. Approximately 2.5% of the patients in the efficacy and extension studies were aged 65 years and older. Analysis of the data did not show an increased risk of hepatic or renal adverse events in these patients.

*Pediatric populations*
Studies in pediatric populations were not conducted.

*Pregnancy and lactation*
Studies in pregnant or lactating women were not performed. However, previous non-clinical data suggest that human *in utero* exposure to naltrexone may have adverse consequences (see Section 7.1.14). Therefore, use of Medisorb Naltrexone in pregnancy should be avoided, unless the potential benefit justifies the potential risk to the fetus.

## 8.4 Pediatrics

The Agency granted the Applicant a waiver from conducting studies of Medisorb Naltrexone in the pediatric population ages 0-11 years, and a deferral from conducting studies in pediatric patients 12 years or older. Upon approval of the NDA, [redacted]

## 8.5 Advisory Committee Meeting

Not applicable.

## 8.6 Literature Review

Not applicable.

## 8.7 Postmarketing Risk Management Plan

Not applicable.

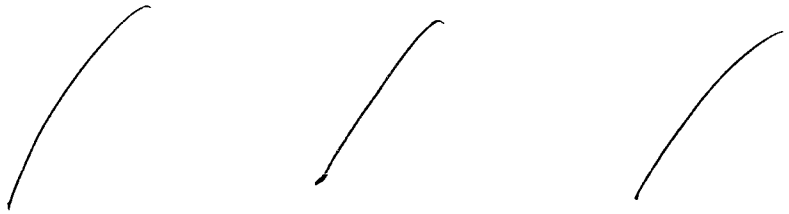
## 8.8 Other Relevant Materials

The following Divisions were consulted regarding the adequacy of the items below:

- Division of Medication Errors and Technical Support (DMETS): Proposed proprietary trade name
- Division of Drug Marketing, Advertising, and Communications (DDMAC): Proposed product labeling
- Division of Surveillance, Research, and Communication Support (DSRCS): Proposed patient package insert

Key recommendations were as follows:

*Proposed proprietary trade name*
Initially, Alkermes proposed VIVITREX® for it s trade name. DMETS did not recommend use of this trade name for several reasons including the following:



Alkermes proposed the trade name VIVITROL® as an alternative to Vivtrex. DMETS found this name acceptable.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

*Efficacy*
The Applicant found Medisorb Naltrexone 380-mg more efficacious than placebo in reducing the event rate of heavy drinking. Also, using a definition (cut-off) for treatment response of at least 1 heavy drinking day per month, the company found a greater proportion of treatment responders in the Medisorb Naltrexone 380-mg group than in the placebo group.

My review of the efficacy of this product was based on an alternate definition of treatment response, namely the absence of any heavy drinking (i.e. zero heavy drinking days) over the treatment period. This analysis found no numerical or statistical differences between either dose of Medisorb Naltrexone (190-mg or 380-mg) and placebo as regards the proportion of patients able to refrain from heavy drinking. However, when the same analysis was performed using the subgroup of patients who were completely abstinent at baseline, the proportion of responders increased greatly, and there was a more considerable difference in response rates between Medisorb Naltrexone groups and the placebo group.

*Safety*
The evaluation of the safety of Medisorb Naltrexone focused on the risks of hepatotoxicity, suicide, and opioid overdose, as well as on the common adverse effects of treatment. Alkermes sought to show that, because the route of naltrexone administration by-passed first pass metabolism, Medisorb Naltrexone was less likely than oral naltrexone to be associated with hepatotoxicity. The risk of opioid overdose in opioid abusers was evaluated because of the long-lasting blockade effects of naltrexone at the opioid receptor – patients who attempt to overcome the blockade effects with higher opioid doses may overdose as the blockade wanes. Opiate blockade is also a potential mechanism for suicide/suicidal behaviors. This is because opioid blockade could induce dysphoria and other mood changes.

From the safety data, Alkermes concluded that the potential serious effects of treatment were eosinophilic and interstitial pneumonia, and that there was not an increased risk of

hepatotoxicity, suicide or opioid overdose. The most common adverse effects of treatment were injection site reactions.

Per my evaluation of the data, Medisorb Naltrexone could potentially cause allergic reactions. Patients treated with the drug were consistently more likely than placebo patients to have inflammatory reactions at the injection site. One patient had a severe hypersensitivity reaction with subsequent tissue necrosis requiring surgical debridement. Other allergic-type reactions to Medisorb Naltrexone were elevated peripheral eosinophils, urticaria, angioedema, and eosinophilic pneumonia. Unlike the Applicant, I considered both serious cases of pneumonia to be eosinophilic pneumonia.

Unfortunately, the available data are insufficient to conclusively show that Medisorb Naltrexone is allergenic. Nevertheless, there is no information to fully rule this possibility out. Until this potential effect is fully evaluated, the risk remains.

Also unlike the Applicant, I found that treatment with Medisorb Naltrexone is associated with a slightly increased risk of AST and ALT compared to placebo. However, this risk is similar to that associated with that of oral naltrexone therapy. Furthermore, patients administered Medisorb Naltrexone were slightly more likely to experience suicidal ideation or suicidal attempts.

### 9.2 Recommendation on Regulatory Action

I recommend against approval of this application for the following reasons:

1. Information regarding the reproductive toxicity, genetic toxicity, and carcinogenetic potential of the combined "naltrexone + PLG" product are lacking.

2. The accuracy and reliability of the efficacy data from the sole efficacy trial are questionable due to irregularities in the conduct of the study.

3. Although pre-specified in the protocol, the primary efficacy endpoint is not easily interpreted clinically and has uncertain utility for clinical practice.

4. When the data were analyzed using the efficacy endpoint currently deemed more clinically meaningful by the Division, there was minimal efficacy across all treatment groups. Furthermore, there was no difference in efficacy between either of the Medisorb Naltrexone groups and the placebo group.

5. The data suggest that Medisorb Naltrexone has allergic potential and that serious and life-threatening allergic reactions are possible. However, there is insufficient information to fully elucidate the underlying mechanism of action, identify the risk factors for an allergic reaction, the steps to be taken to prevent such reactions, or the methods to be used to treat emergent allergic responses.

Ultimately, there is poor support of a benefit following treatment with Medisorb Naltrexone, and multiple concerns regarding the possible risks of this product.

The following will be required should the Applicant resubmit the NDA for review:

- Information regarding the reproductive toxicity, genetic toxicity, and carcinogenetic potential of the combined "naltrexone + PLG" product
- At least one adequate and well-controlled study of Medisorb Naltrexone in a suitable population. Efficacy should be based on a clinically relevant endpoint such as treatment response, where response/success is defined based on a meaningful improvement in alcohol consumption.
- Data describing the type and magnitude of risk of allergic reactions following treatment with Medisorb Naltrexone, as well as predictive and preventative factors, and procedures to treat emergent reactions.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

A formal risk management program for this product is not required. However, labeling should:

- Emphasize the need for clinical monitoring of patients for emergence of depressive symptoms.
- [redacted]
- Caution prescribers and abusers of opioids of the risk of overdose should patients attempt to overcome the blockade effect with increasing doses of opioids. The risk is particularly great as the blockade effect begins to diminish.

### 9.3.2 Required Phase 4 Commitments

- The CYP inhibition studies that the Applicant conducted using fluorogenic substrates were not sufficient to fully describe any inhibitory effects of Medisorb Naltrexone. CYP inhibition studies using conventional substrates and analytical methods should be conducted.

### 9.3.3 Other Phase 4 Requests

None.

2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

## 9.5 Comments to Applicant

1. The data submitted in this application are inadequate to establish the efficacy of Medisorb Naltrexone for the treatment of chronic alcohol dependence. The sole efficacy study failed to show a clinically meaningful difference in efficacy between the Medisorb Naltrexone groups and the placebo group. Conduct at least one additional adequate and well-controlled study using a clinically relevant endpoint such as treatment response, where response/success is defined based on a meaningful improvement in alcohol consumption. Ensure that the methods for collection of drinking data are free from potential bias.

2. The data submitted in this application are inadequate to establish the safety of Medisorb Naltrexone. Specifically, the data do not fully characterize the allergenic potential of Medisorb Naltrexone. Perform at least one additional adequate and well-controlled trial to supplement the primary NDA database to carefully collect and report adverse event data that are consistent with a hypersensitivity response to treatment.

3. To further evaluate the allergenic potential of Medisorb Naltrexone, conduct a trial to ascertain whether patients develtop nlatrexone-specific, naltrexone-carboxymethylcellulose-specific, and carboxymethylcellulose-specific antibodies (IgG, IgM, and IgG) following Medisorb Naltrexone administration. Evaluate whether development of these specific antibodies is associated with adverse events of urticaria and angioedema.

4. Provide non-clinical data regarding the reproductive toxicity, genetic toxicity, and carcinogenicity of Medisorb Naltrexone (i.e. the "naltrexone + PLG" combination).

# 10 APPENDICES

## 10.1 Review of Individual Study Reports

### 10.1.1 Protocol ALK 21-003

"A Phase III, Multi-Center, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of Medisorb Naltrexone in Alcohol Dependent Adults."

Objectives
*Primary*

- To evaluate the efficacy of Medisorb Naltrexone (190- and 380-mg IM Q 4 weeks) versus placebo in adults with alcohol dependency
- To asses the safety and tolerability of repeat IM injections of Medisorb Naltrexone

*Secondary*
To evaluate the clinical efficacy of Medisorb Naltrexone versus placebo as assessed by secondary and exploratory endpoints

- Days to relapse of first heavy drinking event
- Days to relapse to any alcohol consumption
- Number of alcoholic drinks per day
- Percent heavy alcohol drinking days
- Percent days abstinent from alcohol
- Event rate of drinking above the NIAAA-specified "safe drinking" level ( drink/day (women), 2 drinks day (men))
- Event rate of any drinking over 24 weeks of treatment
- Serum GGT and Serum CDT changes over time
- Health care utilization and social functioning
- Time to patient discontinuation

Study design:
This was a Phase 3, multiple-dose, randomized, double-blind, parallel group, placebo-controlled trial conducted at 24 sites in the United States.

Treatment duration: 24 weeks (6 months)

Study population and procedures:
The protocol specified enrollment of 450 patients. Patients would be randomized to Medisorb Naltrexone 190 mg, Medisorb Naltrexone 380 mg, Placebo for Medisorb Naltrexone 190 mg, and Placebo for Medisorb Naltrexone 380 mg in a 2:2:1:1 fashion.

Eligibility criteria were:

- Current diagnosis of alcohol dependency using DSM-IV criteria
- Males or non-pregnant females aged 18 years and over
- Able to provide TLFB alcohol consumption information for the 90 day period prior to detoxification and/or screening
- At least 2 episodes of heavy alcohol drinking (heavy alcohol drinking defined as 4 alcohol drinks/day for women and 5 alcohol drinks/day for men) per week, during the 30 days prior to detoxification and/or screening
- Non-custodial stable residence and a telephone plus one contact with verifiable
- address and telephone number
- Females of childbearing potential: use of adequate contraception

Subjects would be excluded for:

- Clinically significant medical condition or observed abnormalities (including: Physical Exam, ECG, laboratory evaluation, urinalysis findings)
- Evidence of hepatic failure and/or ascites, prolonged prothrombin time (INR $\geq$ 1.7), bilirubin >10% above upper limit of normal and/or esophageal variceal disease.
- Active hepatitis and/or AST, ALT > 3x the upper limit of normal
- History of pancreatitis
- Major depression with suicidal ideation, psychosis, bipolar disorder, or psychiatric disorders that would compromise the patient's ability to complete the study. (Patients with treated depression for which pharmacotherapy has been stable for 8 weeks would be permitted).
- Current dependency (within the previous year) to benzodiazepines, opiates or cocaine by DSM IV criteria
- Use of benzodiazepines within 7 days prior to first dose of study medication
- Treatment with disulfiram or oral naltrexone within 10 days of screening
- Greater than 7 days of inpatient treatment for substance use disorders in the 30 days prior to randomization
- Use of any opiates and/or methadone within 14 days prior to screening or patients likely to require opiate therapy during the study period
- Positive urine toxicological screen for opiates and methadone on the day of randomization
- Receipt of any approved or investigation depot product administered into the gluteal muscle within 6 months of screening
- Participation in a clinical trial of a pharmacological agent within 30 days prior to screening
- Previous enrollment in a Medisorb Naltrexone clinical trial
- Known intolerance and/or hypersensitivity to naltrexone or to polylactide-coglycolide (PLG)
- Any finding that in the view of the Principal Investigator would compromise the subject's ability to fulfill the protocol visit schedule and visit requirements or put the subject at risk
- Treatment with any restricted medications
- Subjects on parole or probation or those with pending legal proceedings that have the potential for incarceration during the study period
- Positive serum or urine pregnancy test (at screening or at each treatment period)
- Lactation

Study medication:
Medisorb Naltrexone is a microsphere-based formulation comprised of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide (PLG). The drug is suspended in an aqueous diluent, and then injected intramuscularly. The 190-mg dose is suspended in 2-mL of diluent, and the 380-mg dose is suspended din 2-mL of diluent. Placebo for Medisorb Naltrexone did not contain any naltrexone, and was administered in either 2-mL or 4-mL injections, to maintain the blind.

Study medication would be administered by the study investigators every 4 weeks. The injections were to the gluteal muscle, and the sites of administration alternated.

Prohibited therapies:
The following medications could not be taken unless they were required to treat an adverse event *and* no other alternative treatment was available:

| | | | |
|---|---|---|---|
| Acamprosate, | disulfiram, | oral naltrexone, | tranylcypromine, ondansetron, |
| phenelzine, | selegiline, | sodium valproate, | valproic acid, divalproex sodium, |
| carbamazepine, | | methadone, | levomethadyl acetate/LAAM, |
| bupenorphine, | alprazolam, | chlordiazepoxide, | clonazepam, clorazepate, |
| diazepam, | estazolam, | flurazepam, | halazepam, lorazepam, |
| oxazepam, | prazepam, | quazepam, | temazepam, triazolam, |
| zolpidem tartrate | | | |

Study procedures:
*Clinic visits*:
Patients were to return to the clinic weekly for 4 weeks after receiving the first injection for study evaluations and biopsychosocial support therapy (BRENDA). After receiving the 2nd and 3rd injections, patients would return to the clinic biweekly for study evaluations and biopsychosocial support. After the 4th, 5th and 6th injections, patients would be seen every 4 weeks for study treatment and biopsychosocial support, and would be contacted by telephone two weeks after each injection.

*Screening:*
Screening could begin up to 14 days prior to randomization. Detoxification must have been completed by Day -7.

Subjects were to provide a medical and substance abuse history, as well as physical examination. Patients' BAC level was to be 0 prior to obtaining informed consent and drinking history, as well as participation in study procedures. The TLFB-90 would be completed to provide data on drinking patterns for the 90 days prior to screening (or detoxification). Laboratory testing would also comprise hematology, chemistry, LFTs, CDT, urinalysis, and pregnancy testing. An ECG would also be obtained. Subjects were to complete baseline questionnaires regarding their general health status, social functioning, and healthcare utilization. The standardized psychosocial counseling (BRENDA) would be provided.

Patients meeting all entry criteria would be randomized. Randomization to study treatment was to be stratified by 4 factors: treatment site, gender, lead-in-drinking prior to randomization, and treatment goal of total abstinence (yes/no).

*Non-dosing visits (Days 7, 14, 21, 42, 70)*
Visits would start with BAC testing and TLFB determination of alcohol consumption since the last assessment. The injection site would be evaluated, and any adverse events or changes in concomitant medications would be noted. Counseling using BRENDA would be given.

*Treatment visits (Days 28, 56, 84, 112, 140)*
Procedures for non-dosing days would be followed. Additional assessment would be vital signs, laboratory testing, and completion of the general health, social functioning, and healthcare utilization questionnaires. Use of any non-study psychosocial support would be recorded. The next dose of study drug would be administered.

*Telephone contact visits (Days 98, 126, 154)*
Patients' drinking behavior since the last visit would be evaluated using TLFB. Use of any non-study psychosocial support and concomitant medications, as well as occurrence of any adverse events would be recorded.

*Study termination (Day 168)*
The termination visit was to occur 4 weeks after the last injection, or if a subject prematurely discontinued trial participation. Procedures done during the screening process would be repeated.

Subjects who discontinued study treatment early could continue study participation and receive psychosocial counseling with BRENDA. These subjects would follow the same visit and procedure schedule (except for administration of study drug). Use any pharmacological treatments for alcohol dependency would result in termination from the trial.

## Appendix Table 10.1.1.a Study Procedures – ALK 21-003

| Visit Week | wk 0[a] Day -14 | wk1 Day 0 | wk 2 Day 7 | wk 3 Day 14 | wk 4 Day 21 | wk 5 Day 28 | wk 7 Day 42 | wk 9 Day 56 | wk 11 Day 70 | wk 13 Day 84 | wk 15 Day 98 | wk 17 Day 112 | wk 19 Day 126 | wk 21 Day 140 | Day 154 | Day 168 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Procedures** | **Screen[b]** | **T 1** | | | | **T 2** | | **T 3** | | **T 4** | **Phone** | **T 5** | **Phone** | **T 6** | **Phone 2-weeks post last inj.** | **4-weeks post last inj.** |
| **Informed Consent** | X | | | | | | | | | | | | | | | |
| **Past Medical History** | X | | | | | | | | | | | | | | | |
| **Demographics** | X | | | | | | | | | | | | | | | |
| **Physical Exam** | X | X | | | | | | | | | | | | | | X |
| **Vital signs** | X | X | | | | X | | X | | X | | X | | X | | X |
| **Randomization** | | X | | | | | | | | | | | | | | |
| **Hematology[b] and Biochemistry[c]** | X | X[d] | | | | X | | X | | X | | X | | X | | X |
| **Urinalysis** | X | | | | | X | | X | | X | | X | | X | | X |
| **Urine Pregnancy** | X[e] | X | | | | X | | X | | X | | X | | X | | |
| **Urine Drug Screen** | | X | | | | | | | | | | | | | | |
| **ECG** | X | | | | | | | | | | | | | | | X |
| **SF-36v2™ Health Survey** | X | | | | | X | | X | | X | | X | | X | | X |
| **Drinking Behavior – Time Line Follow-back** | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Breath/Saliva Alcohol Test** | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| **Baseline BRENDA Assessment** | X | | | | | | | | | | | | | | | |
| **Psychosocial Support/BRENDA** | | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| **Documentation of Non-Study Psych/Soc Support** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Recording of Social Functioning and Healthcare Utilization** | X | | | | | X | | X | | X | | X | | X | | X |
| **Administration of Medisorb Naltrexone or Placebo for Medisorb Naltrexone** | | X[g] | | | | X | | X | | X | | X | | X | | |
| **Concomitant Meds** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Adverse Events** | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Study Completion Status** | | | | | | | | | | | | | | | | X[h] |

a) Up to 14 days prior to Day 0
b) Hematology: hemaglobin, red blood count, total and differential (absolute) white count, platelets, prothrombin time (INR value)
c) Chemistry: electrolytes (sodium, potassium, calcium), creatinine, total protein, total bilirubin, ALT, AST, GGT, carbohydrate deficient transferrin (CDT), LDH, alkaline phosphatase, , CPK, glucose, blood urea nitrogen (BUN), albumin, inorganic phosphorus, uric acid, PTT(at screening only)
d) Selected chemistry only: CDT and GGT
e) Serum or urine pregnancy test acceptable at Screening for women of child bearing potential
f) 90 day timeline follow back drinking capture
g) Continued Eligibility confirmed prior to dosing
h) Enrollment into the Extension Study or Premature Discontinuation

Statistical Analysis

*Efficacy measures*

- Time Line Follow Back -> a method to aid patient's recall of drinking, and to retrospectively estimate alcohol consumption
- SF-36v2™ Health Survey
- Social Functioning and Healthcare Utilization Questions
- BAC
- CDT
- GGT

Definition of an alcohol drink:
1 standard drink of alcohol (13.6 g absolute alcohol) was equivalent to:
- Beer (5%): 12 oz (341 mL)
- Wine (12-17%): 5 oz or Fortified Wine: 3 oz
- Hard liquor (80-proof): 1½ oz

Malt liquor conversion:

$$\frac{(\#\text{ ounces of malt liquor consumed})(4/3)}{12} = \#\text{ standard drinks}$$

*Primary efficacy outcome: Event rate of heavy drinking*
The primary endpoint was to be the event rate of heavy drinking in the Medisorb Naltrexone group versus the placebo group. A heavy drinking event was defined as at least 4 drinks/day (women) and 5 drinks/day (men). The event rate was to be calculated over the duration of treatment (i.e. over 24 weeks or up to the time of treatment discontinuation). In the analysis, patients randomized to either volume of placebo (2-mL or 4-mL) would be combined to form one placebo group.

The primary analysis for the primary endpoint would be based an intent-to treat approach, and on the Andersen-Gill model. The secondary analysis of the primary endpoint would include adjustments for treatment site.

*Secondary, Supplemental, and Exploratory Analyses*

- Time (days) to relapse to the first heavy drinking event
- Time to relapse to any alcohol drinking
- Number of alcohol-containing drinks/drinking day
- Percent heavy drinking days
- Percent days abstinent from alcohol
- Event rate of drinking above NIAAA-specified "safe drinking" over 24 weeks ($\geq$ 1 drink/day (females) and $\geq$ 2 drinks/day (males))
- Event rate of any drinking over 24 weeks
- Serum GGT and CDT
- Healthcare utilization and functioning

- Time to patient discontinuation

*Sample size calculation*
A sample size of 450 patients was calculated assuming a study power of approximately 90%, to detect a log event-rate ratio of 0.45 to 0.50, using a two-sided test at $\alpha$ =0.05. The study needed to observe approximately 151 independent heavy drinking events, requiring enrollment of approximately 150 patients per treatment group, accounting for dropouts.

The power projection assumed that the proportion of patients who would abstain from heavy drinking would be 0.795 at 24 weeks in one of the two Medisorb Naltrexone treatment groups as compared to 0.600 in the placebo group and 0.600 in the other Medisorb Naltrexone group (a constant log hazard ratio of 0.45 for one of two Medisorb Naltrexone treatment groups relative to placebo for Medisorb Naltrexone). The power projection was based only on the time to the first event. However, in the primary analysis all recurrent heavy drinking events for each patient would be included. The Applicant anticipated that this analysis would be more powerful than the conventional survival analysis of the time to the first heavy drinking event.

*Missing data and multiplicity*
The original protocol did not address the issue of multiple efficacy comparisons, or how missing data would be handled in the statistical analysis.

Key Protocol Amendments:

*Amendment 1- April 3, 2002*
- Three exclusion criteria were added/modified
  - Urine toxicological screen positive for opiates
  - Use of Ambien (zolpidem tartrate) within 7 days of the 1st dose of study drug
  - Use of oral naltrexone or disulfiram within 10 days of screening
- The following were added to the list of prohibited medications:
  - mephobarbital, phenobarbital, gabapentin, tiagabine, felbamate, levetiracetam, oxcarbazepine, primidone, topiramate, zonisamide, lamotrigine, methsuximide, and ethosuximide
- Study visit procedures were added/modified:
  - Screening procedures included the Alcohol Dependence Scale Questionnaire
  - Documentation of non-study psychosocial support was removed from the protocol
  - At each clinic visit, patients' BAC level had to be $\leq$ 0.02 prior to collection of self-reported drinking data

*Amendment 2 – June 7, 2002*
This amendment comprised administrative changes, as well as the clarification that preparation and administration of the study drug, provision of psychosocial support (BRENDA), and collection of TLFB data was to be done by different individuals.

*Amendment 3 – September 30, 2002*
This amendment included an increase in the number of enrolled patients from 450 to 600.

- Alkermes recalculated the sample size after encountering "challenges" studying its population. The power projections for this study (and therefore the sample size) were based on the detection of log hazard ratio methods for the first heavy drinking event and were extended to recurrent events.

  The impact of the increased sample size was anticipated to be that the log event-rate ratio for detection of heavy drinking events would increase from approximately (0.45 to 0.50) to (0.50 to 0.55) under the same assumptions stated in the original protocol. This would allow for the observation of a different effect size between the treatment groups.

  The new power projection assumed that the proportion of patients who would be abstinent from heavy drinking would be 0.775 at 24 weeks in one of the two Medisorb Naltrexone treatment groups as compared to 0.600 in the placebo group and 0.600 in the other Medisorb Naltrexone group (a constant log hazard ratio of 0.50 for one of two Medisorb Naltrexone treatment groups relative to placebo for Medisorb Naltrexone).

Changes to the statistical analysis plan

*Handling of missing data*

In response to the Division's request for pre-specification of how missing data would be defined and handled in the analysis (Advice Letter, 4/2/02 and 9/24/03), Alkermes proposed the following:

> In the primary analysis of the primary endpoint, no imputations would be performed for days in which drinking data were unavailable. Specifically, a counting process style of data input to the Cox model was used. Each subject contributed drinking event intervals (in days) for the days in which data were collected. Time for which data were not collected was not included in any of the intervals.

The Division found that, in the case of a missing interval in the middle of the study, the proposed approach could underestimate the number of heavy drinking events. A sensitivity analysis assuming the worst case (i.e. heavy drinking) for missing data in the middle of the study was recommended. In response, Alkermes constructed a sensitivity analysis where subject that were missing in the middle of the study (i.e. before a subject completed or discontinued) were imputed as heavy drinking days.

*Responder analysis*

As recommended by the Division, in order to provide additional perspective on the meaningfulness of the primary analysis of the primary endpoint, the Applicant performed a supplemental responder analysis based on the response profile of the treated subjects. The following response categories were constructed, and subjects were classified into one of these categories depending on their overall individual percent heavy drinking days reported during participation in the study:

- 0, no heavy drinking days per month

- > 0 and ≤ 1 heavy drinking day per month
- > 1 and ≤ 2 heavy drinking days per month
- > 2 and ≤ 3 heavy drinking days per month
- > 3 and ≤ 4 heavy drinking days per month
- > 4 heavy drinking days per month.

*Rules to handle TLFB data:*
Several data handling rules for the primary endpoint were utilized. A key assumption was that the applicable follow-up period after the last dose was defined as up to + 30 days. TLFB data collected after 30 days follow-up on the last dose was to be excluded from the drinking data for the primary analysis of the primary endpoint, the assumption being that the treatments were effective for up to a month post injection. Subject data would not be excluded from analysis if the follow-up period between doses was greater than 30 days. This scenario is reflective of the real life circumstance that subjects will not always stay on schedule.

**Appendix Table 10.1.1.b: Rules for TLFB Drinking Data**

| | ISSUE | PROPOSAL |
|---|---|---|
| 1 | TLFB Data Precision | Round to 1 decimal place |
| 2 | Subjects treated but no TLFB reported | Censored at Day 0 (Technically, these subjects are recorded as having experienced 1 day on study without an event.) |
| 3 | Missing TLFB data days | Exclude these days from analysis |
| 4 | More than 1 TLFB drinking value reported (at separate study visits) for same calendar day | Take value reported on most proximal study visit, unless study visit falls on day in question—then take next visit's reported value |
| 5 | TLFB from subjects dosed out of window, or who skipped doses | Use all data as reported |
| 6 | TLFB that extends beyond the applicable follow-up period after the last dose. This includes subjects who receive all 6 doses. | Use all data as reported up until the last dose + 30 days |
| 7 | Subjects discontinue treatment but continue to provide TLFB data as per agreement | Use all data as reported up until the last dose + 30 days |
| 8 | TLFB reported by subjects who detox then continue treatment thereafter | Use all data as reported |

*Comparative placebo group*
The Division did not agree with the Applicant's plan to pool the 2-mL and 4-mL placebo groups based on the assumption that the groups would have comparable outcomes. The Division argued that the two groups were distinct placebos corresponding to the two active treatment groups. Pooling them was reasonable only if the outcomes were similar, but this could not be presumed a priori. The Division required that the statistical analysis plan incorporate a method to decide whether or not pooling of the placebo groups was appropriate or not. Unless there was positive

evidence of comparable outcomes, the Applicant was to conduct comparisons of the 390-mg Medisorb Naltrexone group with the 4-mL placebo group, and of the 190-mg group with the 2-mL placebo group.

**Study Results**

The first and last doses of study drug were administered on February 21 2002 and August 20 2003, respectively. The last subject assessment occurred on September 24, 2003.

Enrollment:

Twenty-four sites in the United States participated in the trial. Enrollment at each site was as follows:

| Site # | # Patients Enrolled | Site # | # Patients Enrolled |
|---|---|---|---|
| 202 | 29 | 218 | 31 |
| 207 | 12 | 219 | 6 |
| 208 | 32 | 220 | 13 |
| 209 | 39 | 221 | 26 |
| 210 | 38 | 223 | 6 |
| 211 | 25 | 224 | 31 |
| 212 | 30 | 225 | 40 |
| 213 | 33 | 226 | 8 |
| 214 | 35 | 227 | 20 |
| 215 | 36 | 228 | 17 |
| 216 | 30 | 229 | 17 |
| 217 | 46 | 230 | 27 |
| ***Total Enrolled: 627*** | | | |

Protocol violations:

Each of the study sites had at least 1 protocol violation. Site #230 had the greatest number of deviations, and also the highest rate of deviations per subject. The lowest deviation rate occurred at site #209.

Appendix Table 10.1.1.c summarizes the number of subjects with an important protocol deviation or violation, by treatment group. (Note that a subject may have had multiple deviations/violations, and that subject would be counted only once in each category.) The table shows that "out of window dosing" was the most common protocol violation, occurring in a similar number of patients across each of the Medisorb Naltrexone and the pooled placebo groups. The Medisorb Naltrexone 190-mg group had the highest number of misclassifications in stratification. Otherwise, the groups had similar numbers and types of protocol violations and deviations.

**Appendix Table 10.1.1.c Protocol violations and deviations – ALK21-003**

| | Placebo 2mL | Placebo 4mL | 190 mg | 380 mg | Total |
|---|---|---|---|---|---|
| Out of window dosing* | 27 | 44 | 74 | 70 | 215† |
| Treatment blind broken | 0 | 0 | 0 | 1 | 1 |
| Misclassified for stratification at randomization | 4 | 5 | 12 | 7 | 28‡ |
| Did not meet all entry criteria | 5 | 5 | 10 | 8 | 28 |
| Used prohibited medications during study ‖ | 10 | 7 | 17 | 17 | 51 |

*Doses were to be administered every 28 days ± 3 days.
† Out of 567 total subjects. This total excludes subjects who withdrew after receiving Dose 1 and before receiving Dose 2 and therefore differs from the ITT population total of 624.
‡ Two additional subjects, 1 in the 2 mL placebo group and 1 in the 190 mg group, were misclassified at randomization; however, the IVRS entry was corrected before the study was unblinded. This is explained in greater detail in Appendix 16.1.9.2 (Statistical Supplement) of the ALK21-003 CSR.
‖ Includes 3 subjects (1 in the 190 mg group and 2 in the 380 mg group) who used Baclofen. Before unblinding the study, Alkermes became aware of literature reports of the use of Baclofen for the treatment of alcohol dependence. Because of the potential for confounding the efficacy data, it was decided to exclude these subjects from the efficacy analysis. These 3 subjects did not actually violate the protocol, but were retrospectively selected for exclusion from the efficacy analyses, based on their use of this medication.

During study ALK21-003, minor procedural protocol deviations (e.g. unsigned lab reports, procedures not done, done out of order, or done differently than specified in the protocol) were documented by the study monitors on a tracking spreadsheet and/or in monitoring reports. These types of deviations were not documented on a case report form or otherwise formally tracked in the study database.

Assuming that these minor deviations were similar across treatment groups, and based upon the information about the major protocol deviations, it is not expected that the protocol deviations/violations significantly impacted the primary efficacy outcome.

*Protocol violations noted upon DSI inspection*
DSI inspected four sites for adherence to protocol requirements and noted irregularities at all four sites. The most notable violations were (1) performance of the psychosocial counseling and the TLFB data collection by the same person, as well as (2) performance of the physical examination and adverse event assessment by the same person providing psychosocial counseling. The former violation was concerning for possible bias in the number of drinks either reported or recorded. However, these violations were not considered to not have systematically introduced bias in favor of the Medisorb Naltrexone groups, and would thus to have had limited effects on the primary efficacy outcome (see Sections 4.4 and 6.1.4.1for details).

Blinding:

The treatment blind was broken for one patient (ALK21-003-211-002/MFM) due to bone marrow suppression. The patient was randomized to Medisorb Naltrexone 380 mg. All Alkermes and study personnel remained blinded to the patient's treatment assignment except for the patient's hematologist, one site sub-investigator, and the unblinded study drug administrator.

Subject disposition:
Patient disposition was tabulated based on treatment completion status and on study completion status. Subjects who discontinued use of the study drug were given the option of continuing participation in all other aspects of the study. Overall, there were 627 subjects randomized, and 624 who took at least 1 dose of medication. The 3 subjects who were not administered any study medication were in the Medisorb Naltrexone 380-mg group and were withdrawn due to "investigator judgment."

A total of 402 patients (64%) completed treatment. Among the 222 subjects (36%) who prematurely discontinued treatment, 49 opted to continue with other aspects of the study, including provision of TLFB data: 13 in the placebo group, 14 in the Vivitrex 190 mg group, and 22 in the Vivitrex 380 mg group. Of those 49 subjects, 33 subsequently completed the study.

The Applicant was asked to tabulate patient disposition, using all available data sources (e.g. termination visit sheet, adverse event sheet, drug administration sheet) to determine the actual reason for dropout, particularly in cases where dropout is listed as "lost to follow up," "investigator decision," or "other." Reclassification of the reason for dropout was to be done if necessary. Also, patients who dropped out due to events related to alcohol use (e.g. "alcoholism," "detoxification") were to be reclassified as dropping out due to lack of efficacy.

Appendix Table 10.1.1.d shows the patient disposition, and the reasons for early study termination. The most common reason for trial discontinuation was loss to follow up (83 patients, 13%), followed by adverse events (52 patients, 8%), withdrawal of consent (42 patients, 7%), and lack of treatment efficacy (34, 5%). More patients in the Medisorb Naltrexone 190-mg group withdrew for adverse events (15%) compared to patients in the 380-mg and placebo groups (12 and 13%, respectively). On the other hand, twice as many placebo patients withdrew due to lack of efficacy (8%) than did patients in the Medisorb Naltrexone groups (4% each).

## Appendix Table 10.1.1.d: Subject disposition – Treatment completion status - ALK21-003

| | | Placebo | | | Medisorb Naltrexone | |
|---|---|---|---|---|---|---|
| | **All subjects** | **2 mL** | **4 mL** | **Pooled** | **190-mg** | **380-mg** |
| N Randomized | 627 | 105 | 104 | 209 | 210 | 208 |
| | | | | | | |
| N Dosed | 624 | 105 | 104 | 209 | 210 | 205 |
| | | | | | | |
| N(%) [1] completed treatment 2 | 402 (64) | 62 (59) | 73 (70) | 135 (65) | 137 (65) | 130 (63) |
| | | | | | | |
| Reason [3] for discontinuation, N(%) [1] | | | | | | |
| Lost to follow-up | 83 (13) | 19 (18) | 9 (9) | 28 (13) | 31 (15) | 24 (12) |
| Adverse events | 58 (8) | 7 (7) | 6 (6) | 13 (6) | 12 (6) | 27 (13) |
| Subject withdrew consent | 42 (7) | 8 (8) | 5 (5) | 13 (6) | 14 (7) | 15 (7) |
| Lack of efficacy | 34 (5) | 7 (7) | 9 (9) | 16 (8) | 9 (4) | 9 (4) |
| Investigator judgment | 4 (1) | 1 (1) | 1 (1) | 2 (1) | 2 (1) | 0 |
| Protocol violation | 2 (0) | 0 | 0 | 0 | 2 (1) | 0 |
| Other [#] | 5 (1) | 1 (1) | 1 (1) | 2 (1) | 3 (1) | 0 |

[1] Percentages are out of number of subjects dosed
[2] Includes Subject 214-013 who missed one injection and enrolled to ALK21-003EXT
[3] Reason for discontinuation was reclassified using all applicable information on each subject
[#] "Other" includes: incarceration (n = 2); too far out of dosing window to receive an injection (n = 3)

(Source: Applicant's Table 1.1.1, Applicant's July 29 2005 response to an Information Request, P. 6)

Extent of exposure:
As shown in Appendix Table 10.1.1.e (below), of the 624 patients treated with study drug, 410 patients (64.3%) were administered all 6 six doses. The percentage of subjects who took all 6 doses was similar across treatment groups (approximately 64%). Due to the long-acting properties of Medisorb Naltrexone, exposure was expected to last approximately 1 month after dosing. Therefore, subjects who took all 6 doses would have been exposed for 24 weeks.

Among the 223 subjects who did not receive all 6 doses, 57 subjects (9.1%) received 1 dose; 68 (10.9%) received 2; 36 (5.8%) received 3; 38 (6.1%) received 4; and 24 subjects (3.9%) received 5 doses. Overall, subjects had a median of 140 days from first dose to last dose, representing an exposure of over 168 days. Some subjects had one or more late doses of study medication, resulting in a maximum of 205 days from first to last dose.

Demographics:
Baseline characteristics were similar for the 3 treatment groups. Mean age was 44.7 years with a range of 19-79 years. The proportion of males to females was approximately 2:1 for all treatment groups. Most subjects were Caucasian (83.5%).

The majority of subjects (571, 91.5%) reported lead-in drinking. During the 30 days prior to the first dose, subjects reported a mean of 22.9 drinking days, and a mean of 19.5 heavy drinking days. This corresponds to 76.4% drinking days and 64.9% heavy drinking days over that one month period. Treatment goals were similar among treatment groups. Nearly three quarters of subjects reported baseline treatment goals of total abstinence (43.3%) or occasional use (30.6%). Nearly half of the subjects (48.6%) were enrolled at an addiction treatment center; 34.0% enrolled at a research center; and 17.5% enrolled at a combination addiction/research center.

The ADS questionnaire was added to the protocol in April 2002, following initiation of enrollment. Subjects enrolled prior April 2002 date did not complete the ADS questionnaire. ADS questionnaires were collected for 306 of the 624 subjects (49%) in the ITT population. The mean ADS score among subjects was 17.1; this score was similar among treatment groups.

## Appendix Table 10.1.1.e Applicant's Analysis of Extent of Exposure – ALK21-003

| | Treatment Group | | | |
|---|---|---|---|---|
| | All Subjects | Placebo | 190mg | 380mg |
| No. of Subjects in the Intent-to-Treat Population | 624 | 209 | 210 | 205 |
| Total No. of Injections Received: | | | | |
| 1 Dose | 57 ( 9.13) | 15 ( 7.18) | 23 (10.95) | 19 ( 9.27) |
| 2 Doses | 68 (10.90) | 25 (11.96) | 18 ( 8.57) | 25 (12.20) |
| 3 Doses | 36 ( 5.77) | 9 ( 4.31) | 13 ( 6.19) | 14 ( 6.83) |
| 4 Doses | 38 ( 6.09) | 18 ( 8.61) | 12 ( 5.71) | 8 ( 3.90) |
| 5 Doses | 24 ( 3.85) | 8 ( 3.83) | 7 ( 3.33) | 9 ( 4.39) |
| 6 Doses | 401 (64.26) | 134 (64.11) | 137 (65.24) | 130 (63.41) |
| Days from First Dose to Last Dose | | | | |
| N | 624 | 209 | 210 | 205 |
| Mean | 108.76 | 109.94 | 109.04 | 107.27 |
| Std.Dev. | 52.83 | 50.72 | 53.85 | 54.09 |
| Median | 140 | 140 | 140 | 140 |
| Min-Max | 0-205 | 0-186 | 0-204 | 0-205 |

SOURCE: Section 14.3 Table 14.3.1
[Percentages are out of the number of subjects in the Intent-to-Treat Population

(Source: Applicant's Table 40, Module 5, Clinical Study Report, ALK21-003, P. 121)