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1. Executive Summary

This review report is for two studies ALO-01-07-106 and ALO-01-07-205.

The primary objective of study ALO-01-07-106 was to determine the relative drug-liking and euphoric effects of intravenous (IV) morphine alone to IV morphine combined with IV naltrexone as reflected in pharmacodynamic (PD) measures following single IV bolus doses. The study demonstrated that the euphoric effects of intravenous (IV) morphine combined with IV naltrexone were statistically significantly lower than those of IV morphine alone in both measures High VAS and Cole/ARCI Stimulation Euphoria Scale.

The primary objectives of study ALO-01-07-205 were to determine the relative pharmacodynamic effects and safety of crushed and whole ALO-01 compared to Morphine Sulfate IR (MSIR) and to Placebo and of crushed ALO-01 to whole ALO-01. The study results showed that administration of ALO-01 crushed and ALO-01 whole resulted in lower effects on five subjective primary measures (Drug Liking VAS, Cole/ARCI Stimulation-Euphoria Scale, Cole/ARCI Abuse Potential, Subjective Drug Value, and ARCI MBG), one objective primary measure (Pupillometry) and two subjective secondary measures (High VAS and Bad Drug Effects VAS) of response than administration of MSIR but higher than administration of Placebo. No significant difference between crushed ALO-01 and whole ALO-01 was found for any of the PD measures of interest.

2. Review Report on Study ALO-01-07-106

2.1 Overview

Objective of the study

The primary objective of study ALO-01-07-106 is to determine the relative drug-liking and euphoric effects of intravenous (IV) morphine alone to IV morphine combined with IV naltrexone as reflected in pharmacodynamic (PD) measures following single IV bolus doses.

Study design

This study was a randomized, placebo-controlled, double-blind, double-dummy, single-dose, three way crossover study. The study subjects were opioid experienced, non-dependent male subjects.

The following Latin square design was used:

Sequence	Period		
	1	2	3
1	MP	PP	MN
2	MN	MP	PP
3	PP	MN	MP

where MN: Morphine 30 mg IV + Naltrexone 1.2 mg IV;
MP: Morphine 30 mg IV + IV Naltrexone Placebo;
PP: IV Morphine Placebo + IV Naltrexone Placebo.

In this study, subjects participated in an in-patient Naloxone Challenge, an in-patient Drug Discrimination Phase, and out-patient treatment. The washout period between two treatments was 6-days.

Endpoints interest of the CSS

There were many endpoints in this study. The CSS is interested in the following endpoints:

Primary endpoint: High VAS (Emax), ranged from 0 to 100;

Secondary endpoint: The Cole/ARCI Stimulation Euphoria Scale (Emax), ranged from 0 to 45.

Hypotheses in this study

For each endpoint of interest, the data should provide sufficient evidence that

- MP has significantly greater mean response than PP (to insure the validity of MSIR as the positive control)
- MN has significantly greater mean response than PP
- MN has significantly smaller mean response than MP

The given significance level of each test is 5% (two-sided).

More specifically, for each endpoint of interest, tests of the following null hypotheses were performed:

- the mean response of MP is equal to that of PP
- the mean response of MN is equal to PP
- the mean response of MN is greater than or equal to MP

2.2 Data location

The following was the link of the data sets used in this review.

[\\CDSESUB\IEVSPROD\NDA022321\0014](#)

2.3 Reviewer's analysis on the primary endpoint High VAS

There was no predose response recorded in the dataset for High VAS in the original submission. After this reviewer made the request, the sponsor included a column for predose response in the dataset. However, all predose responses were zero. Therefore, the reviewer's analysis was based on Emax High VAS. As specified in the originally protocol, responses from 26 completers (100% randomized subjects) were used in the analysis.

Figure 1 is a needle chart for three responses to the treatments MN, MP and PP by subjects. From this plot, one may see how each subject responded to the three treatments.

Figure 2 is a plot of treatment differences in Emax High VAS at the subject level. From this plot, one may see the difference in responding to two different treatments by each subject. The mean, standard deviation, minimum, 25th percentile (Q1), median, 75th percentile (Q3) and maximum of the differences in each comparison are listed in Table 1.

Table 1: Summary of treatment differences in Emax of High VAS

Difference	Mean	Std Dev	Min	Q1	Median	Q3	Max
MN – MP	-54.38	25.89	-93	-78	-61.5	-30.5	-7
MN – PP	30.92	26.26	0	11	22.5	43	93
MP – PP	85.31	13.09	55	75.75	88.5	97.75	100

It can be seen from Table 1 that approximate 75% of subjects had a smaller response to the treatment MN than to the treatment MP by 30.5 points. From the summary of the results for the comparisons MN vs. PP and MP vs. PP, one may see that the difference MP – PP was approximately 2.75 and 3.93 times higher than the difference MN – PP in mean and median respectively. Note that MN – PP and MP – PP equal MN and MP respectively, because the response to the treatment PP was equal to zero for all subjects in this study. Therefore, the

reviewer concurs with the statement “The mean Emax of morphine was nearly 3-fold greater than that of morphine/naltrexone” in the proposed label.

A mixed-effect model with period, sequence and treatment as fixed effects, and subject nested with sequence as a random effect was used in the analysis. SAS proc mixed was used to evaluate the significance of the fixed effects, and the Shapiro-Wilk *W*-test in SAS proc univariate was used to assess the normality assumption of the study model. It was found that residuals of the model for Emax High VAS had a significant non-normal distribution, thus ranks of responses within subjects were used in the statistical analysis for this endpoint. The statistically significantly lower median response in the treatment MN than in the treatment MP, and higher median responses in both treatments MP and MN than in PP were demonstrated in the study. All p-values were less than 0.0001. Detailed percentage of reduction of Emax High VAS in MN to MP ((MP – MN)/MP*100%) is summarized in Table 2.

From Table 2, one may see that approximately 69% (18/26) of the subjects had at least 50% reduction in Emax High VAS by taking IV morphine combined with IV Naltrexone compared to by taking IV morphine alone, and approximately 54% (14/26) of the subjects had at least 70% such a reduction.

Table 2: Summary of percentage of reduction of Emax High VAS in IV morphine combined with IV Naltrexone to IV morphine alone

Reduction (%)	10	20	30	40	50	60	70	80	90	100
# of patients	24	24	21	20	18	17	14	10	4	2
Percent	92	92	81	77	69	65	54	38	15	8

* Percentage of subjects

Figure 3 shows the treatment difference in Emax High VAS between MN and MP for each subject. From this figure, one may see that all subjects (26 subjects) had higher response to the treatment MP than to the treatment MN, and the magnitudes of these differences.

2.4 Reviewer’s analysis on change from predose Emax Cole/ARCI Stimulation Euphoria Scale

Similar descriptive statistics were calculated for change from predose Emax Cole/ARCI Stimulation Euphoria Scale. The results are shown in Figure 4, Figure 5 and Figure 6, and Table 3 and Table 4.

Table 3: Summary of treatment differences in change from predose Emax of the Cole/ARCI Stimulation Euphoria Scale

Difference	Mean	Std Dev	Min	Q1	Median	Q3	Max
MN – MP	-14.81	14.99	-36	-24	-19	-7	35
MN - PP	12.04	10.74	-12	3	12	18	39
MP - PP	26.85	10.32	4	22	28	34	43

Table 4: Percentage of Reduction of change from pre-dose Emax of Cole/ARCI Stimulation Euphoria Scale in IV Naltrexone 1.2 mg from Morphine 30 mg IV

Reduction (%)	10	20	30	40	50	60	70	80	90	100
# of patients	22	20	18	17	14	11	7	5	3	3
Percent	85	77	69	65	54	42	27	19	12	12

* Percentage of subjects

It was found that three out of twenty six subjects (approximately 12%) had their change from pre-dose Emax to the MN as high as or higher than that to MP (See [Figure 4](#) and [Figure 6](#)). But there were also 3 subjects (approximately 12%) who had 100% reduction of change from pre-dose Emax of ARCI Stimulation Euphoria Scale in MN from MP (See [Table 4](#)). The mean or median change from pre-dose response to MN was more than 2 fold of that to MP (See [Table 3](#)).

The same statistical model as the model used for Emax of High VAS was used for testing the difference in mean change from pre-dose Emax of ARCI Stimulation Euphoria Scale between treatments. Statistically significant differences were detected in the comparison between MN and MP, MN and PP, and MP and PP, with a p-value less than 0.0001 in each case.

2.5 Conclusion

The euphoric effect of intravenous (IV) morphine alone was statistically significantly higher than that of IV morphine combined with IV naltrexone. The mean Emax of IV morphine was nearly 3-fold greater than that of IV morphine/naltrexone for the primary endpoint High VAS, and was more than 2-fold greater than that of IV morphine/naltrexone for the secondary endpoint, namely in the change pre-dose Cole/ARCI Stimulation Euphoria Scale. Both IV morphine combined with IV naltrexone and IV morphine had significantly higher median response of Emax High VAS and higher mean response of change from pre-dose Emax Cole/ARCI Stimulation Euphoria Scale than the Placebo.

3. Review Report on Study ALO-01-07-205

3.1 Overview

Objectives of the study

The primary objectives were to determine the relative pharmacodynamic effects and safety of crushed and whole ALO-01 compared to Morphine Sulfate IR (MSIR) and to Placebo, and of crushed ALO-01 to whole ALO-01.

The secondary objectives were to determine the relative bioavailability of plasma morphine from crushed and whole ALO-01 compared to MSIR and from crushed ALO-01 to whole ALO-01, and to determine the relative bioavailability of plasma naltrexone and 6-β-naltrexol from crushed ALO-01 to whole ALO-01.

Study design

This was a randomized, double-blind, triple-dummy, 4-way crossover, single center study.

Study subjects were recreational, non-dependent, opiate users. There were total of 5 study sessions: Qualification Session and 4 Treatment Sessions.

The qualifying session was designed to identify those subjects who could (1) tolerate a single dose of morphine (120 mg) and (2) distinguish between a single dose of morphine and placebo on at least four of the following six measures: Visual Analog Scale (VAS) for Drug Liking, VAS for Overall Drug Liking, VAS for High, VAS for Good Effects, Addiction Research Center Inventory (ARCI)–Morphine-Benzedrine Group (MBG), and Subjective Drug Value (SDV). During the qualifying session, all eligible subjects randomly received single doses of MSIR 120 mg containing beverage and placebo beverage, administered once over 2 days.

During each treatment session, all eligible subjects received two whole capsules (with active drug or placebo) and two beverages (with active drug and/or placebo) orally. All eligible subjects received each of the four following treatments, one per treatment session:

Treatment A: 2 x Placebo capsules (whole) + ALO-01 2 x 60 mg capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

Treatment B: 2 x 60 mg ALO-01 (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

Treatment C: 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + 120 mg Morphine Sulfate IR in apple juice (Beverage 2)

Treatment D: 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

Eligible subjects were randomized to a treatment sequence based on a computer generated randomization schedule. Based on this randomization code, the study drugs were prepared for each subject. Subjects received all four treatments in the order specified by the treatment sequence according to a Williams Square design as follows:

Sequence/Period	1	2	3	4
1	A	B	D	C
2	B	C	A	D
3	C	D	B	A
4	D	A	C	B

where

A : ALO-01 120 mg crushed

B : ALO-01 120 mg whole

C : MSIR solution 120 mg

D: Placebo

The washout period between dosing was 14 to 21 days.

Study Population

A total of a 132 subjects were screened for inclusion in this study. Of the 132 subjects screened, 73 were eligible for inclusion, and 58 of those subjects were randomized and dosed in the qualifying session. Forty-three subjects passed the qualifying session and were eligible for the treatment period. Only 58 of 73 subjects were randomized and dosed in the qualification because a sufficient number of subjects was eligible for the treatment period, and continuation of the qualifying session was not necessary. Of the 43 subjects who passed the screening/qualifying period, 32 subjects were randomized into the treatment period. **All 32 (100.0%) subjects received all doses of the study drugs and completed all treatment sessions of the study without any major protocol violations.**

Data from 32 (100.0%) subjects were included in the sponsor's statistical analysis.

Primary endpoints : Drug Liking VAS, Cole/ARCI Stimulation Euphoria Scale, Cole/ARCI Abuse Potential, Subjective Drug Value, ARCI MBG, and Pupillometry

Secondary endpoints interest of the CSS: Bad Drug Effects VAS

Secondary endpoints interest of this reviewer

Because High VAS was considered in study ALO-01-106, this reviewer added High VAS in her analysis.

Hypotheses in this study

For each endpoint of interest, the data should provide sufficient evidence that

- MSIR has significantly greater mean response than placebo (to insure the validity of MSIR as the positive control)
- ALO-01 whole has significantly smaller mean response than MSIR
- ALO-01 crushed has significantly smaller mean response than MSIR
- there is a significant difference between ALO-01 whole and ALO-01 crushed
- ALO-01 whole has significantly greater mean response than placebo
- ALO-01 crushed has significantly greater mean response than placebo

The given significance level of each test is 5% (two-sided).

More specifically, for each endpoint of interest, tests of the following null hypotheses were performed:

- the mean response of MSIR is equal to that of placebo
- the mean response of ALO-01 whole is greater than or equal to MSIR
- the mean response of ALO-01 crushed is greater than or equal to MSIR
- there is no difference in mean between ALO-01 whole and ALO-01 crushed
- the mean response of ALO-01 whole is equal to that of placebo
- the mean response of ALO-01 crushed is equal to that of placebo

where

ALO-01 – formally known as Kadian NT

ALO-01 crushed – ALO-01 120 mg crushed treatment group
ALO-01 whole – ALO-01 120 mg whole treatment group.

3.2 Data location

The following was the link of the data sets used in this review.

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3.3 Reviewer's analysis

The reviewer's analyses were based on 32 completers (100% randomized subjects).

Table 5 shows the descriptive statistics mean, standard deviation (Std Dev), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3) and maximum (Max) for each treatment for each primary variable, for a secondary variable interest of the CSS, and for a secondary variable of interest to this reviewer. The descriptive statistics in the table were calculated based on change from predose Emax for the endpoints except the endpoints Drug Liking VAS, Subjective Drug Value and Bad Drug Effects VAS, for which the calculation was based on Emax.

From Table 5, one may see that ALO-01 crushed had similar results to ALO-01 whole. ALO-01 crushed, ALO-01 whole and MSIR had much higher values for both mean and median responses than the Placebo. Although ALO-01 both crushed and whole had lower mean and median responses than MSIR, for most endpoints, they had same maximum responses as MSIR.

A mixed linear model with period, treatment, sequence as fixed effects and subject nested within sequence as a random effect was used in the reviewer's analyses.

SAS proc mixed was used to evaluate the significance of the fixed effects, and the Shapiro-Wilk *W*-test in SAS proc univariate was used to assess the normality assumption of the study model. It was found that only the residuals for Bad Drug Effects VAS were significantly non-normally distributed. Thus the Wilcoxon signed-ranks test was used in the statistical analysis for Bad Drug Effects VAS. P-values from the pairwise comparisons of treatments are listed in Table 6. Detailed results were shown in Appendix I-IV.

From Table 6, one may see that the study passed the validation test for all the endpoints of interest. No significant difference in mean (or median for Bad Drug Effects VAS) response was found between treatment A (ALO-01 crushed) and treatment B (ALO-01 whole). Both treatments A and B had significantly lower mean (or median for Bad Drug Effects VAS) responses than treatment C (MSRI), and had significantly higher mean (or median for Bad Drug Effects VAS) responses than treatment D (Placebo).

3.4 Conclusion

Administration of ALO-01 crushed and ALO-01 whole resulted in lower effects on five subjective primary endpoints (VAS Drug Liking, Cole/ARCI Stimulation-Euphoria Scale, Cole/ARCI Abuse Potential, Subjective Drug Value, and ARCI MBG), one objective primary endpoint (Pupillometry) and two subjective secondary endpoints (VAS High and VAS Bad Drug Effects) of response than administration of MSIR but higher than administration of Placebo. No

significant difference between crushed ALO-01 and whole ALO-01 was found for any of the PD measures of interest.

Table 5: Summary of descriptive statistics for Emax (N=32)

Endpoint	TRT	Mean	Std Dev	Min	Q1	Median	Q3	Max	
Primary Endpoints	VAS Drug Linking	A	68.06	17.51	50	51.25	62	79.5	100
		B	67.59	13.12	51	56.25	66	74.75	100
		C	89.47	12.63	57	81.75	92.5	100	100
		D	52.19	4.51	50	51	51	51	75
	Subjective Drug Value	A	13.72	16.98	0.25	0.25	4.75	20.38	48
		B	14.22	15.46	0.25	1.06	8.25	20.38	48
		C	28.85	14.55	0.25	20.75	29.25	39.94	48
		D	2.73	7.08	0.25	0.25	0.25	0.25	26.75
	ARCI MBG*	A	9.53	10.41	0	1	5	16.5	35
		B	7.50	10.03	0	0	3	14.25	36
		C	17.28	10.91	0	8	18.5	27.75	36
		D	4.13	6.20	0	0	2	3.75	22
	Cole/ARCI Abuse Potential	A	4.72	4.37	0	1	3.5	8	16
		B	4.28	3.52	0	2	3.5	6	14
		C	6.81	4.12	0	4	5.5	11	16
		D	1.84	2.44	0	0	1	3	12
	Cole/ARCI Stimulation—Euphoria	A	8.44	9.07	0	1	5	14.75	34
		B	7.09	9.65	0	0	3	11	36
		C	15.25	10.51	0	6	14	25	32
		D	4.28	6.35	0	0	2.5	4	22
Pupil Diameter (P _{Cmin})	A	2.07	0.91	0.3	1.4	2	2.88	3.6	
	B	2.08	1.07	0	1.2	2.3	2.85	3.9	
	C	2.71	1.05	0.9	1.73	2.85	3.4	5.1	
	D	0.79	0.50	0.1	0.33	0.75	1.25	1.9	
Secondary Endpoints	VAS High*	A	54.66	34.48	0	17.25	64	82.5	100
		B	60.22	30.47	0	49.5	68.5	81.75	100
		C	90.22	11.68	61	81.5	97	100	100
		D	12.66	23.49	0	0	1	10.25	70
	VAS Bad Drug Effects	A	20.91	31.63	0	0	2	41.75	100
		B	23.13	31.49	0	0	5.5	49.5	100
		C	35.66	34.63	0	0	36.5	63.25	100
		D	8.03	17.52	0	0	0	3.5	51

* Results are based on change from predose Emax

Table 6: Pairwise comparisons of treatment difference in mean Emax (or median change from pre-dose Emax): p-values

Comparison	Primary Endpoint						Secondary	
	Liking	Euphoria	Potential	Value	MBG	Pupil	Bad**	High
C > D (Validation)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
A ≠ B	0.7143	0.4410	0.5366	0.8622	0.2152	0.2109	0.7126	0.3318
A > D	<0.0001	0.0019	<0.0001	0.0001	0.0005	<0.0001	0.0001	<0.0001
B > D	<0.0001	0.01525	0.0002	<0.0001	0.0149	<0.0001	0.0025	<0.0001
A < C	<0.0001	<0.0001	0.0005	<0.0001	<0.0001	<0.0001	0.0230	<0.0001
B < C	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0170	<0.0001
W-test p-value***	0.2662	0.8990	0.2823	0.0831	0.9118	0.8663	0.0010	0.4876

Liking: Drug Liking VAS

Euphoria: Cole/ARCI-Stimulation-Euphoria Scale

Potential: Cole/ARCI-Abuse Potential

Value: Subjective Drug Value

MBG: ARCI MBG

Bad: Bad Drug Effects VAS

High: High VAS

Pupil: Pupillometry

* Null hypotheses are listed on page 9

** P-values from Wilcoxon signed rank test

*** P-values from Shapiro-Wilk test

A: ALO-01 crushed

B: ALO-01 whole

C: MSIR

D: Placebo

Appendix

Appendix I: Results from analyses on change from predoxe Emax for Cole/ARCI-Stimulation-Euphoria (ARCIS006), Cole/ARCI-Abuse Potential (ARCIS007), and MBG: ARCI MBG (ARCIS010), and High VAS (GVAS01)

Obs	NAME	TRT	Estimate	StdErr	tValue	Probt	Lower	Upper
1	ARCIS006	A	8.5565	1.7651	4.85	<.0001	5.0494	12.0637
2	ARCIS006	B	7.3659	1.7679	4.17	<.0001	3.8531	10.8786
3	ARCIS006	C	15.1990	1.7645	8.61	<.0001	11.6929	18.7051
4	ARCIS006	D	3.9411	1.7699	2.23	0.0285	0.4244	7.4578
5	ARCIS007	A	4.6789	0.6484	7.22	<.0001	3.3906	5.9672
6	ARCIS007	B	4.2642	0.6483	6.58	<.0001	2.9760	5.5523
7	ARCIS007	C	6.9777	0.6497	10.74	<.0001	5.6867	8.2686
8	ARCIS007	D	1.7355	0.6489	2.67	0.0089	0.4462	3.0249
9	ARCIS010	A	9.6081	1.7965	5.35	<.0001	6.0386	13.1777
10	ARCIS010	B	7.5847	1.7967	4.22	<.0001	4.0148	11.1547
11	ARCIS010	C	17.2556	1.7957	9.61	<.0001	13.6875	20.8237
12	ARCIS010	D	3.9890	1.7982	2.22	0.0291	0.4160	7.5620
13	GVAS01	A	54.5844	4.4401	12.29	<.0001	45.7620	63.4067
14	GVAS01	B	60.1633	4.4372	13.56	<.0001	51.3468	68.9798
15	GVAS01	C	90.1264	4.4448	20.28	<.0001	81.2946	98.9581
16	GVAS01	D	12.8760	4.5000	2.86	0.0053	3.9346	21.8174

Obs	NAME	TRT	_TRT	Estimate	StdErr	tValue	Probt	Lower	Upper
1	ARCIS006	A	B	1.1907	1.5384	0.77	0.4410	-1.8662	4.2475
2	ARCIS006	A	C	-6.6424	1.5387	-4.32	<.0001	-9.6999	-3.5850
3	ARCIS006	A	D	4.6154	1.5486	2.98	0.0037	1.5385	7.6924
4	ARCIS006	B	C	-7.8331	1.5428	-5.08	<.0001	-10.8987	-4.7676
5	ARCIS006	B	D	3.4247	1.5574	2.20	0.0305	0.3303	6.5192
6	ARCIS006	C	D	11.2579	1.5417	7.30	<.0001	8.1945	14.3212
7	ARCIS007	A	B	0.4147	0.6686	0.62	0.5366	-0.9137	1.7431
8	ARCIS007	A	C	-2.2988	0.6707	-3.43	0.0009	-3.6314	-0.9662
9	ARCIS007	A	D	2.9433	0.6688	4.40	<.0001	1.6145	4.2722
10	ARCIS007	B	C	-2.7135	0.6702	-4.05	0.0001	-4.0452	-1.3818
11	ARCIS007	B	D	2.5286	0.6690	3.78	0.0003	1.1994	3.8578
12	ARCIS007	C	D	5.2421	0.6723	7.80	<.0001	3.9063	6.5780
13	ARCIS010	A	B	2.0234	1.6209	1.25	0.2152	-1.1974	5.2442
14	ARCIS010	A	C	-7.6475	1.6226	-4.71	<.0001	-10.8715	-4.4235
15	ARCIS010	A	D	5.6191	1.6279	3.45	0.0009	2.3845	8.8537
16	ARCIS010	B	C	-9.6709	1.6228	-5.96	<.0001	-12.8954	-6.4464
17	ARCIS010	B	D	3.5957	1.6284	2.21	0.0298	0.3601	6.8314
18	ARCIS010	C	D	13.2666	1.6228	8.18	<.0001	10.0421	16.4911
19	GVAS01	A	B	-5.5789	5.7169	-0.98	0.3318	-16.9382	5.7803
20	GVAS01	A	C	-35.5420	5.7170	-6.22	<.0001	-46.9016	-24.1824
21	GVAS01	A	D	41.7084	5.8082	7.18	<.0001	30.1676	53.2493
22	GVAS01	B	C	-29.9630	5.7180	-5.24	<.0001	-41.3247	-18.6014
23	GVAS01	B	D	47.2874	5.7983	8.16	<.0001	35.7663	58.8084
24	GVAS01	C	D	77.2504	5.8215	13.27	<.0001	65.6832	88.8176

Obs	Variable	W-Statistic	p-value
1	ARCIS006	0.99442	0.89902
2	ARCIS007	0.98729	0.28231
3	ARCIS010	0.99460	0.91118
4	GVAS01	0.99002	0.48757

Appendix II: Results from analyses on Emax for Drug Liking VAS (Liking) and subjective Drug Value (Prcross).

Obs	NAME	TRT	Estimate	StdErr	tValue	Probt	Lower	Upper
1	LIKING	A	68.0625	2.1815	31.20	<.0001	63.7286	72.3964
2	LIKING	B	67.5938	2.1815	30.99	<.0001	63.2599	71.9276
3	LIKING	C	89.4688	2.1815	41.01	<.0001	85.1349	93.8026
4	LIKING	D	52.1875	2.1815	23.92	<.0001	47.8536	56.5214
5	PRCROSS	A	13.7188	2.4208	5.67	<.0001	8.9094	18.5281
6	PRCROSS	B	14.2188	2.4208	5.87	<.0001	9.4094	19.0281
7	PRCROSS	C	28.8516	2.4208	11.92	<.0001	24.0422	33.6609
8	PRCROSS	D	2.7266	2.4208	1.13	0.2630	-2.0828	7.5359

Obs	NAME	TRT	_TRT	Estimate	StdErr	tValue	Probt	Lower	Upper
1	LIKING	A	B	0.4688	2.7503	0.17	0.8651	-4.9953	5.9328
2	LIKING	A	C	-21.4063	2.7503	-7.78	<.0001	-26.8703	-15.9422
3	LIKING	A	D	15.8750	2.7503	5.77	<.0001	10.4110	21.3390
4	LIKING	B	C	-21.8750	2.7503	-7.95	<.0001	-27.3390	-16.4110
5	LIKING	B	D	15.4063	2.7503	5.60	<.0001	9.9422	20.8703
6	LIKING	C	D	37.2813	2.7503	13.56	<.0001	31.8172	42.7453
7	PRCROSS	A	B	-0.5000	2.8718	-0.17	0.8622	-6.2053	5.2053
8	PRCROSS	A	C	-15.1328	2.8718	-5.27	<.0001	-20.8381	-9.4276
9	PRCROSS	A	D	10.9922	2.8718	3.83	0.0002	5.2869	16.6974
10	PRCROSS	B	C	-14.6328	2.8718	-5.10	<.0001	-20.3381	-8.9276
11	PRCROSS	B	D	11.4922	2.8718	4.00	0.0001	5.7869	17.1974
12	PRCROSS	C	D	26.1250	2.8718	9.10	<.0001	20.4197	31.8303

Obs	Variable	W-Statistic	p-value
1	GVAS03	0.96132	0.00104
2	LIKING	0.98701	0.26617
3	PRCROSS	0.98178	0.08306

Appendix III: Analysis of Emax of Bad Drug Effects

Difference: C-D

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t 4.596354	Pr > t <.0001
Sign	M 8	Pr >= M 0.0004
Signed Rank	S 97	Pr >= S <.0001

Difference: A-D

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t 2.947518	Pr > t 0.0060
Sign	M 7.5	Pr >= M 0.0007
Signed Rank	S 84	Pr >= S 0.0002

Difference: B-D

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t 2.685421	Pr > t 0.0115
Sign	M 4.5	Pr >= M 0.0784
Signed Rank	S 76	Pr >= S 0.0050

Difference: A - B

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t -0.33685	Pr > t 0.7385
Sign	M -0.5	Pr >= M 1.0000
Signed Rank	S -12.5	Pr >= S 0.7126

Difference: A-C

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t -2.24363	Pr > t 0.0321
Sign	M -2	Pr >= M 0.5413
Signed Rank	S -69	Pr >= S 0.0460

Difference: B-C

Tests for Location: Mu0=0

Test	-Statistic-	-----p Value-----
Student's t	t -1.89028	Pr > t 0.0681
Sign	M -4.5	Pr >= M 0.0931
Signed Rank	S -68.5	Pr >= S 0.0339

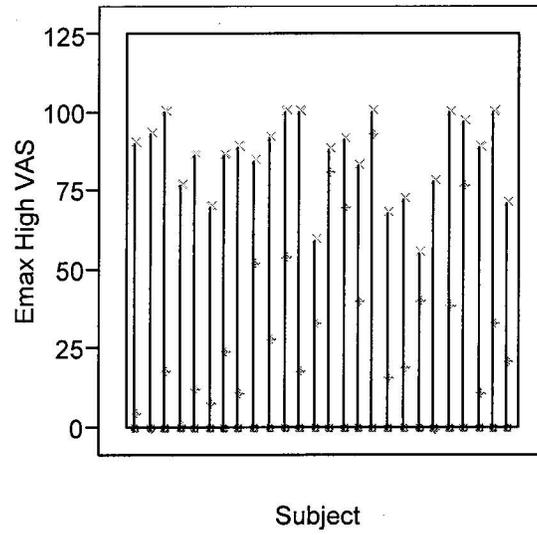
Appendix IV: Results from analyses on change from predose Emax for Pupillometry

Obs	trt	Estimate	StdErr	tValue	Probt	Lower	Upper
1	A	2.0140	0.1240	16.24	<.0001	1.7676	2.2605
2	B	2.1842	0.1243	17.57	<.0001	1.9371	2.4312
3	C	2.7200	0.1239	21.95	<.0001	2.4738	2.9662
4	D	0.7380	0.1240	5.95	<.0001	0.4916	0.9845

Obs	trt	_trt	Estimate	StdErr	tValue	Probt	Lower	Upper
1	A	B	-0.1701	0.1350	-1.26	0.2109	-0.4384	0.09815
2	A	C	-0.7060	0.1342	-5.26	<.0001	-0.9726	-0.4393
3	A	D	1.2760	0.1340	9.52	<.0001	1.0096	1.5423
4	B	C	-0.5358	0.1344	-3.99	0.0001	-0.8029	-0.2688
5	B	D	1.4461	0.1350	10.71	<.0001	1.1779	1.7144
6	C	D	1.9820	0.1342	14.77	<.0001	1.7153	2.2486

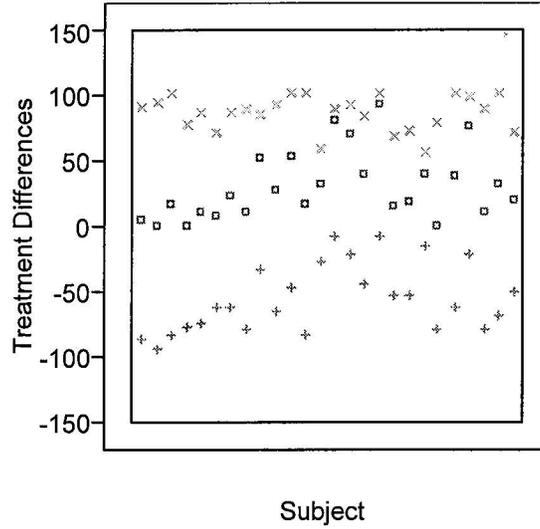
Obs	w-Statistic	p-value
1	0.99399	0.86628

Figure 1: Needle Chart of Emax High VAS by Subject



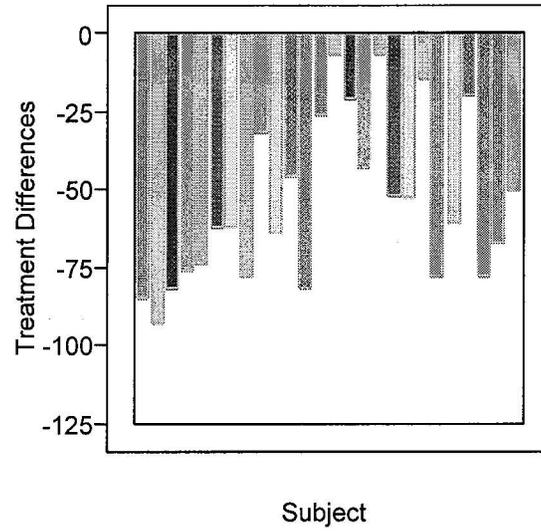
Red: MN Green: MP Blue: PP

Figure 2: Comparison of Treatment Differences in Emax High VAS by Subject



Red: MN – MP; Blue: MN – PP; Green: MP – PP

Figure 3: Treatment Difference in Emax High VAS between MN and MP by Subject



Subject Number	2	3	6	7	8	9
	10	12	13	15	16	19
	20	21	22	23	25	26
	27	28	29	30	31	33
	34	40				

Figure 4: Needle Chart of Emax Cole/ARCI Stimulation Euphoria Scale by Subject

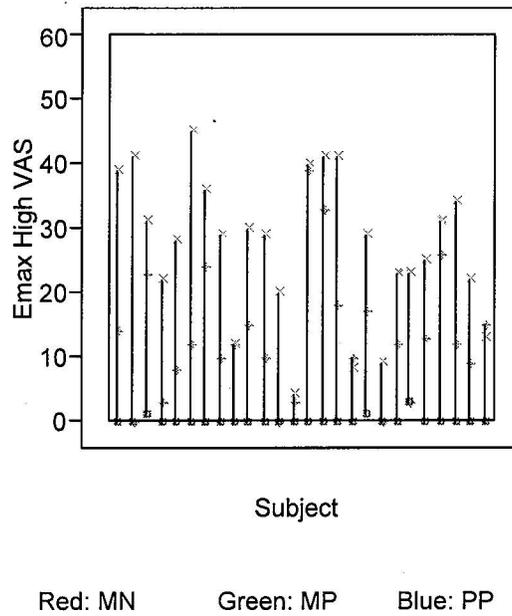


Figure 5: Comparison of Treatment Differences in Emax Cole/ARCI Stimulation Euphoria Scale by Subject

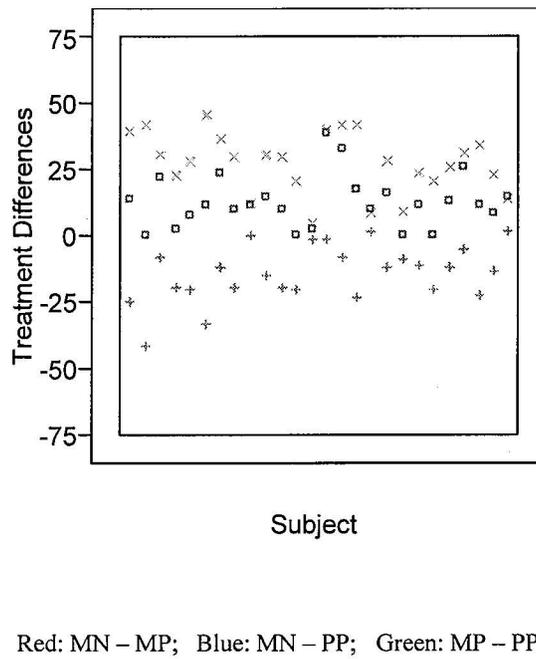
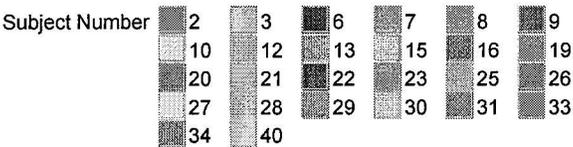
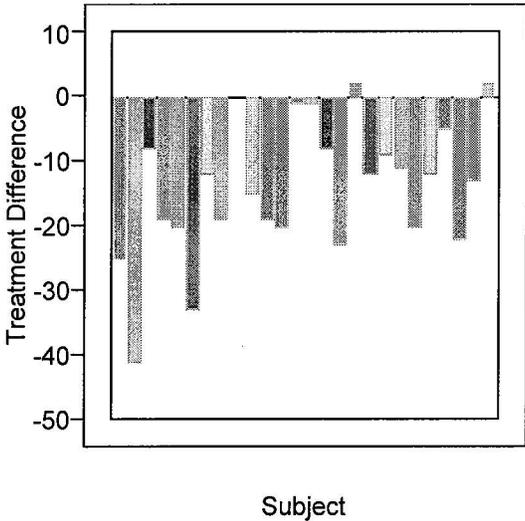


Figure 6: Treatment Difference in ARCI Cole Stimulation Euphoria Scale between MN and NP



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Ling Chen
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Stella Machado
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 22-321 / 00

Drug Name: Kadian NT (morphine sulfate plus naltrexone hydrochloride extended-release) capsules

Indication(s): treatment of moderate to severe chronic pain

Applicant: Alpharma Pharmaceuticals LLC

Date(s): Letter date: 6/30/08
PDUFA date: 12/30/08

Review Priority: Priority

Biometrics Division: Division of Biometrics II

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Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

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Keywords: New formulation; clinical study; NDA review

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

This application requests consideration of Kadian NT (morphine sulfate plus naltrexone hydrochloride extended-release) capsules for the indication of treatment of moderate to severe chronic pain. Kadian (morphine sulfate) capsules are currently approved and marketed for this indication. The intent of the applicant in developing this new formulation is to reduce the risk of diversion and non-medical use. According to the applicant, the naltrexone component blocks the effect of the morphine sulfate if the capsules are crushed.

The applicant submitted efficacy results from a single Phase 3 randomized, double-blind, placebo-controlled clinical study (study #301). A special protocol agreement (SPA) was reached on December 14, 2006 with the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). The efficacy results indicated that the Kadian NT treatment group had a statistically significantly greater reduction in average pain from baseline to end of 12-week maintenance than the placebo group. The secondary endpoints provided supportive evidence of a treatment effect for Kadian NT.

The efficacy and safety results were presented to the Anesthetic and Life Support Drugs Advisory Committee on November 14, 2008. DAARP sought advice on the safe use of Kadian NT, if approved. The advisory committee was not asked to vote, but did give feedback suggesting that this formulation offered some benefits with regard to safe use and reducing diversion.

1.2 Brief Overview of Clinical Studies

Study #301 was a randomized withdrawal study which enrolled patients with painful osteoarthritis of the knee or hip. After an open-label titration period of up to 6 weeks, patients who responded to Kadian NT were randomly assigned to blinded treatment during the 12-week maintenance period. After randomization, patients either continued on the same dose of Kadian NT or received placebo (following a 2-week down-titration period).

The primary endpoint was defined as the mean change from baseline to the end of the maintenance period in the weekly average pain intensity. Pain was measured using the Brief Pain Inventory (BPI) questionnaire, using an 11- point scale with 0 = "no pain" and 10 = "pain as bad as you can imagine". The BPI short form assesses average pain in last 24 hours, worst pain in last 24 hours, least pain in last 24 hours, and pain right now. The first item was used in the calculation of the primary efficacy outcome, and the latter three were used in the calculation of secondary outcomes to assess efficacy.

For the efficacy endpoints, the primary analyses used the intent-to-treat (ITT) patient population, defined as all patients who were randomized, received at least one dose of study treatment and had at least one postdose diary pain assessment. Only one randomized patient was not included

in the ITT population, due to a malfunction of the electronic pain diary.

Support for efficacy was tested by the pairwise comparison of the Kadian NT group to the placebo group. An analysis of covariance (ANCOVA) model was used for the primary efficacy endpoint with terms for treatment and baseline average pain score.

1.3 Statistical Findings

In study #301, the Kadian NT group was statistically significantly better than the placebo group for the mean change in average pain from baseline to the end of the maintenance period. The mean change in the Kadian NT group was -0.2 units compared to +0.3 units in the placebo group. The negative change for the Kadian group represents a continued reduction in average pain on the maintenance dose, while the positive value for the placebo group represents an increase in pain after withdrawing for Kadian NT titration dose. Additional secondary endpoints also supported efficacy for Kadian NT. I conclude Kadian NT is efficacious for this indication.

2. Introduction

2.1 Overview

Kadian NT is a new formulation of an existing approved drug (Kadian; morphine sulfate) with the addition of naltrexone. Morphine and naltrexone are combined in a coated, multiple layer pellet, and each capsule contains the specified dose of pellets. The extended-release capsule is taken orally.

The applicant is requesting approval for use in adult patients experiencing moderate to severe chronic pain. The clinical studies assessed its use in a single patient population – adults with painful osteoarthritis of the hip or knee.

The applicant has submitted a single Phase 3 study to support this application. It was a randomized, double-blind, placebo-controlled, parallel arm, randomized withdrawal study in adult patients. My statistical review focuses on this study, referred to as study #301. The clinical development plan and efficacy study design were discussed with DAARP at the pre-IND meeting on March 16, 2005. The patient population, endpoints, imputation methods and analyses for this study protocol were submitted to DAARP for advice, and a Special Protocol Agreement (SPA) was reached on December 14, 2006. The applicant followed the advice received.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room (edr) in SAS transport

format. All necessary documentation, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path location \\Cdsesub1\evsprod\NDA022321\0000\m5\datasets\alo-knt-301. The information needed for this review was contained in modules 1, 2.5, and 5.3.5.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study ALO-KNT-301 (conducted 1/07 to 11/07)

Design

Study 301 was a randomized, double-blind, parallel arm, multi-center study, conducted at 74 centers in the United States. It was a randomized withdrawal study design, in which all eligible patients at screening were enrolled in an open-label titration phase and received Kadian NT for up to 6 weeks. Treatment responders were then randomized to the double-blind 12-week maintenance phase. Efficacy was assessed at the end of the maintenance phase in terms of continued pain relief from the level achieved during titration.

Patients were adults with osteoarthritis in at least one hip or knee joint. The affected joint with the most pain at screening was identified as the target joint. At the screening baseline, a patient had to have an average pain score of ≥ 5 on the 11-point scale to be enrolled for initial treatment.

During the titration phase, the patients were started on 20 mg BID (40 mg/day) and could increase by increments of 20 mg daily at weekly visits, up to a maximum dose of 80 mg BID (160 mg/day). Back titrations were also allowed until the tolerated effective dose was determined. Kadian NT doses were available in units of 20, 30, 40, 50, 60 or 80 mg capsules. Titration had to be completed within 45 days of enrollment.

A patient who received adequate pain relief was classified as a responder if the average pain score was ≤ 4 on the 11-point scale during the four days prior to a clinic visit and the average pain score was at least a 2-point reduction from the screening baseline. All responders from the titration phase who met all other eligibility criteria were randomly assigned to the double-blind maintenance phase, during which they either continued on the same tolerated effective dose of Kadian NT or received a blinded 2-week down titration followed by placebo.

The primary endpoint was the change from randomization baseline to week 12 of the maintenance period in the average pain intensity score on the Brief Pain Inventory (BPI) scale. It is an 11-point scale, with 0 = no pain and 11 = worst pain (pain as bad as you can imagine). Pain scores are recorded daily in an electronic diary and averaged over each week of the study. Other secondary endpoints from the BPI scale were the least pain over the last 24 hours, the worst pain over the last 24 hours, and current pain.

For the efficacy endpoints, the primary analyses used the intent-to-treat (ITT) patient population defined as all patients who were randomized, received at least one dose of study treatment and had at least one postdose diary pain assessment. This definition was a slight change from the ITT definition in the SPA, which did not include the last phrase regarding at least one postdose diary pain assessment. This slight change appeared to have been necessitated because the electronic diary for one patient malfunctioned and all pain diary data for that subject (173-0004) was lost.

In the protocol, the applicant planned to randomize a total of 400 patients, 200 per group, assuming an effect size (mean treatment group difference / pooled SD) = 0.33 and power of at least 90%. The actual number of patients was only 344, 86% of planned, and the observed effect size was .25 (0.5/2).

Patient Disposition

A total of 344 patients qualified during the titration period and were randomized using a 1:1 ratio to the two treatment arms for the maintenance period. A total of 136 patients discontinued during the maintenance period. The reasons are shown in Table 1. A higher percent of the dropouts in the Kadian NT group were due to adverse events, while a higher percentage in the placebo groups were due to lack of efficacy. This was not unexpected. The differences in the reasons for dropouts were taken into account in the imputation decision rules for the efficacy analyses, described in the next section.

Table 1: Patient Disposition (Study 301)

	Kadian NT	Placebo
Randomized	171	173
Did not have diary pain data	1	0
ITT	170	173
Subjects who discontinued	61 (36%)	75 (43%)
Reasons for discontinuations		
Adverse event	18 (11%)	13 (8%)
Lack of efficacy	6 (4%)	32 (18%)
Non-compliance	9 (5%)	6 (3%)
Investigator's decision	3 (2%)	0
Subject withdrew from study	15 (9%)	12 (7%)
Lost to follow-up	3 (2%)	2 (1%)
Did not meet incl/excl criteria	1 (1%)	2 (1%)
Other	6 (4%)	8 (5%)
Subjects who completed 12-week maintenance period	110 (64%)	98 (57%)

Source: Clinical Study Report Figure 1 and Table 13 narrative

Baseline Demographics

The two treatment groups were balanced with respect to relevant demographic and baseline characteristics. These are shown in Table 2. The randomization plan did not include any strata.

Table 2: Demographic Characteristics at Baseline (All Randomized; Study 301)

	Kadian NT N=171	Placebo N=173
Age (years)		
Mean (SD)	54 (12)	55 (13)
Range	24, 81	21, 85
Age group:		
18-64 yrs	141 (82%)	136 (79%)
≥65 yrs	30 (18%)	37 (21%)
Gender		
Female	106 (62%)	95 (55%)
Male	65 (38%)	78 (45%)
Race		
Caucasian	95 (56%)	87 (50%)
Black/African-American	28 (16%)	28 (16%)
Asian	9 (5%)	15 (9%)
Hispanic/Latino	36 (21%)	40 (23%)
Other	3 (2%)	3 (2%)
BMI (kg/m ²)		
Mean (SD)	32 (6)	33 (7)
Median	31	32
Range	17, 45	17, 53
BMI group:		
≤24.9 kg/m ²	22 (13%)	22 (13%)
25-29.9 kg/m ²	49 (29%)	53 (31%)
≥30 kg/m ²	96 (56%)	92 (53%)
Missing	4 (2%)	6 (3%)
Primary Joint with OA		
Hip		
Right	20 (12%)	24 (14%)

Left Knee	17 (10%)	16 (9%)
Right Left	77 (45%) 57 (33%)	83 (48%) 50 (29%)

Sources: Clinical Study Report Table 14 and SAS datasets

Efficacy Results

The planned analysis for the primary efficacy endpoint was an ANCOVA model with terms for treatment and baseline average pain. The baseline was the average pain at the end of titration, prior to randomization. The same model was applied for the secondary endpoints, using the respective baseline measure.

Prior to enrollment in the titration phase, patients were screened for average pain level to meet eligibility criteria. This was referred to as the screening baseline. After titration, if adequate pain relief had been achieved, the patient was randomized to the maintenance phase. The average pain measurements just prior to randomization were referred to as the randomization baseline.

In the SPA, the following imputation decision rules were agreed upon:

- Screening baseline will be imputed for discontinuations due to adverse events. This imputation rule assigns no efficacy benefit to study drug when the subject discontinues for an adverse event.
- If the results of the COWS questionnaire at discontinuation are worse than at randomization baseline and indicate at least a moderate (score ≥ 13) level of withdrawal symptoms, the following imputation rules will be used.
 - Randomization baseline will be imputed for the placebo group, regardless of the reason for discontinuation, and assigns full efficacy benefit to subjects in the placebo group who discontinue while experiencing at least moderate withdrawal symptoms.
 - The weekly diary BPI pain score in the last 7 days on study will be imputed for discontinuations in the Kadian NT group due to lack of efficacy or administrative reasons. Screening baseline will be imputed for discontinuations in the Kadian NT group due to adverse events. This imputation rule assigns a score that is worse than randomization baseline for subjects who report at least moderate levels of withdrawal symptoms.
- The weekly diary BPI average pain score during the last 7 days on study will be imputed for discontinuations due to lack of efficacy or administrative reasons. This imputation rule assigns the actual pain reported at discontinuation, which for both study drugs will tend to be worse than randomization baseline when open-label Kadian NT is administered but less severe than screening baseline.

The results of the analyses are presented in Table 3. A change in a negative direction indicates an improvement (reduction of pain) from the end of titration to Week 12 of the maintenance period. A change in a positive direction indicates an undesirable outcome (return of pain) from the end of titration to Week 12 of the maintenance period. A negative between-group difference favors Kadian NT over placebo.

The Kadian NT group was statistically significantly different from, and superior to, the placebo group for the change from baseline to end of maintenance period in the average pain intensity. The secondary endpoints were also favorable for the Kadian NT group.

Table 3: Study 301 Efficacy Analysis Results

			Kadian NT N=170	Placebo N=173
Primary Endpoint: <u>Average pain</u> in last 24 hours: Mean change from baseline to Week 12 of maintenance	Baseline Week 12 Change	Mean (SD) Mean (SD) Mean (SD) Difference p-value	3.3 (1.3) 3.1 (2.0) -0.2 (1.9) -0.5 .045	3.2 (1.1) 3.5 (2.1) 0.3 (2.1)
Secondary Endpoints:				
<u>Worst Pain</u> in last 24 hours: Mean change from baseline to Week 12 of maintenance	Baseline Chg at Wk 12	Mean (SD) Mean (SD) Difference	3.6 (1.6) 0.3 (2.0) -0.6	3.5 (1.6) 0.9 (2.0)
<u>Least Pain</u> in last 24 hours: Mean change from baseline to Week 12 of maintenance	Baseline Chg at Wk 12	Mean (SD) Mean (SD) Difference	2.1 (1.4) 0.3 (1.8) -0.5	1.9 (1.3) 0.8 (1.8)
<u>Current Pain:</u> Mean change from baseline to Week 12 of maintenance	Baseline Chg at Wk 12	Mean (SD) Mean (SD) Difference	2.6 (1.6) 0.4 (2.0) -0.5	2.4 (1.5) 0.9 (2.1)

Source: Clinical Study Report Tables 20 and 25 and SAS datasets

Three sensitivity analyses were performed to test the impact of the imputation decision rules on the primary efficacy results. The first approach imputed the randomization baseline for all discontinuations for all reasons. This implies the full benefit of the Kadian NT received during the open-label titration remained even after discontinuation. The p-value for the ANCOVA model for this method was 0.12, which was not unexpected since more patients dropped in the placebo arm. The second sensitivity analysis imputed the screening baseline (no benefit from

study participation) for all discontinuations for all reasons. The p-value for the ANCOVA for this method was 0.049. The final sensitivity analysis imputed the screening baseline (no benefit) for patients who dropped due to adverse events or lack of efficacy, and the randomization baseline (full titration benefit) for all other reasons. The p-value for this approach was 0.005. Overall, these sensitivity analyses confirm that the difference between the groups in the treatment effect was not being influenced inappropriately by the imputation approach used in the primary efficacy analysis.

Dr. Chen identified three patients in the placebo group who experienced withdrawal symptoms after randomization. These patients had Clinical Opiate Withdrawal Scale (COWS) scores ≥ 13 during the 2-week down-titration after randomization. When I checked the observed pain and discontinuation records for these patients, I determined only one (subject ID 173-0004) had discontinued at the time the withdrawal symptoms were observed.

A continuous responder analysis, based on percentage change from baseline, is not applicable to this withdrawal study design because neither the screening nor randomization baseline provides clarity as the denominator. Eligibility required achieving adequate pain relief after titration, so the screening baseline pain score is not the frame of reference to assess efficacy. On the other hand, after titration a randomization baseline score of zero was ideal pain relief. For subjects with a denominator close to zero, very small unit changes result in large percent changes. Another factor is that patients who have no change in pain are classified as not improving, when that is actually a benefit to the patient in this study design. Thus a continuous responder analysis would not provide clear information regarding efficacy.

Instead, I preferred to categorize patients by the direction of change from randomization baseline to Week 12. As shown in Table 4, the percent of patients whose pain did not return (worsen) after randomization was lower in the Kadian NT group than in the placebo group.

Table 4: Study 301 Average Pain in last 24 hours - Change from Randomization to Week 12

	Pain worsened	Pain did not change	Pain improved
Kadian NT N=170	69/170 41%	9/170 5%	92/170 54%
Placebo N=173	88/173 51%	5/173 3%	80/173 46%

Source: D_PREND2 dataset

3.2 Evaluation of Safety

The safety analyses were completed by Dr. Chen. He did not request any additional analyses regarding safety in my review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

I reviewed exploratory analyses for the primary endpoint by age groups, gender, and race. There were no notable differences in the mean changes for the treatments across any of these subgroups. Results for age, gender and race are shown in Table 5.

Table 5: Subgroup Analyses

Primary Endpoint: <u>Average pain</u> in last 24 hrs: Mean change from baseline to Week 12 of maintenance		Study 301 Osteoarthritis of Hip or Knee	
Treatment group:		Kadian NT N=170	Placebo N=173
Age groups			
18-64 years	N Rand. Baseline Mean (SD) Week 12 Mean (SD) Mean change Mean (SD)	140 3.3 (1.2) 3.2 (2.0) -0.1 (1.9)	136 3.2 (1.0) 3.5 (2.1) 0.3 (2.0)
≥65 years	N Rand. Baseline Mean (SD) Week 12 Mean (SD) Mean change Mean (SD)	30 3.3 (1.8) 2.8 (1.9) -0.4 (2.3)	37 3.3 (1.3) 3.4 (2.1) 0.1 (2.1)
Gender			
Female	N Rand. Baseline Mean (SD) Week 12 Mean (SD) Mean change Mean (SD)	105 3.2 (1.3) 3.1 (2.2) -0.1 (2.1)	95 3.3 (1.1) 3.4 (2.1) 0.1 (2.1)
Male	N Rand. Baseline Mean (SD) Week 12 Mean (SD) Mean change Mean (SD)	65 3.5 (1.2) 3.2 (1.9) -0.3 (1.6)	78 3.2 (1.0) 3.7 (2.2) 0.5 (2.0)
Race			
Caucasian	N Rand. Baseline Mean (SD) Week 12 Mean (SD) Mean change Mean (SD)	127 3.3 (1.4) 3.1 (1.9) -0.2 (1.8)	121 3.1 (1.1) 3.5 (2.1) 0.4 (1.9)

Non-Caucasian	N	43	52
	Rand. Baseline Mean (SD)	3.3 (1.1)	3.5 (0.9)
	Week 12 Mean (SD)	3.3 (1.9)	3.6 (1.9)
	Mean change Mean (SD)	0 (2.3)	0.1 (2.4)
Initial Opioid Status Experienced	N	41	42
	Rand. Baseline Mean (SD)	3.6 (1.3)	3.3 (1.0)
	Week 12 Mean (SD)	3.7 (2.3)	4.0 (2.0)
	Mean change Mean (SD)	0.1 (2.2)	0.7 (1.8)
Naïve	N	125	129
	Rand. Baseline Mean (SD)	3.2 (1.3)	3.2 (1.1)
	Week 12 Mean (SD)	2.9 (1.8)	3.4 (2.2)
	Mean change Mean (SD)	-0.3 (1.8)	0.1 (2.1)

Sources: ISE Table 4 and SAS datasets

4.2 Other Special/Subgroup Populations

Dr. Chen did not request any additional subgroup analyses.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Study 301 was conducted as planned following the SPA, and any protocol amendments did not impact the analysis or interpretation of the results. Dropouts were identified as a concern due to anticipated differences in the reasons for discontinuations for the treatment groups. The imputation process to adequately address the dropout concern was pre-specified in the SPA, and missing data was handled appropriately.

5.2 Label Issues

The applicant's proposed label reports the results from the analysis in the Clinical Studies section (14.1). The study design, patient population, and endpoints for the efficacy study are appropriately described. I have the following suggestions regarding the reporting of the results:

1. Remove p-values for all endpoints.
2. I would prefer the results for the primary endpoint appear in the text or table rather than the bar graphs shown in Figure 6.
3. Remove the following statements which report secondary endpoints:

4. Figure 7 shows a continuous responder analysis curve with percent change from baseline calculated from screening (visit X) to Week 12 (visit Y+12). This was not the timeframe for the efficacy assessments, so the graph is not applicable. A continuous responder curve is not appropriate for the withdrawal study design and should not be included in the label.
5. Remove section 14.2 regarding efficacy results from the long-term, open-label study.

5.3 Conclusions and Recommendations

The goal of this study was to investigate the efficacy of the Kadian NT for treatment of chronic moderate to severe pain in adults with osteoarthritis of the hip or knee. The efficacy results indicated that Kadian NT was statistically superior to the placebo for mean change in average pain intensity from baseline to Week 12 of the maintenance period. Additional clinically relevant secondary endpoints provided supportive evidence of a treatment effect for Kadian NT versus placebo. Based on my review of this study, I conclude there is sufficient evidence of efficacy for Kadian NT for this indication.

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/s/

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