CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206544Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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:	NDA 206-544/0000
Supplement Number:	NA
Drug Name:	Morphine ARER (Abuse Resistant Extended Release) Tablets
Indication(s):	Human abuse liability
Applicant:	Inspirion Delivery Technologies, LLC
Date(s):	Date of Document: 11/21/2014 Consult received date: 12/12/2014 Consult desired completion date: 2/27/2015
Review Priority:	P
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OD/CSS Silvia Calderon, Team Leader, Pharmacologist, OD/CSS Michael Klein, Ph.D., Director, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints	

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EXECUTIVE SUMMARY

Data of NDA206544 were submitted by Inspirion Delivery Technologies, LLC (the sponsor) for requesting approval of Morphine ARER (Abuse Resistant Extended Release) (IDT-001), an abuse-deterrent formulation of morphine sulfate extended-release tablets, for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The study M-ARER-002 included in this NDA needed a statistical review for drug abuse liability.

Confirmation of abuse-potential:

The Study M-ARER-002 was a phase 1 study of a mono-center, randomized, double-blind, double-Dummy, placebo- controlled, single-Dose, four-way crossover study to determine the abuse potential and safety of equivalent doses of crushed and intact Morphine ARER (Abuse Resistant Extended Release) (IDT-001), an abuse-deterrent formulation of morphine sulfate extended-release tablets, compared with crushed MS contin® and placebo in opioid experienced, non-dependent subjects following intranasal administration. The data of this study was submitted by Inspirion Delivery Technologies, LLC, and was evaluated

The numbers of completers were 25 (93%) with a total of 27 subjects randomized to the treatment phase. The number of completers assured the analysis power greater than 80% for detecting a significant difference between crushed intranasal IDT-001 and crushed intranasal MS Contin with 80% power under the sample size assumptions at a two-sided alpha level of 0.05 on the Drug Liking (at the moment) VAS.

This reviewer confirmed the sponsor's results about the abuse-deterrent properties of crushed intranasal and intact oral IDT-001 relative to the positive control, crushed intranasal MS contin, based on the pre-defined primary and secondary endpoints: Drug Liking (at the moment) VAS, areas under the Drug Liking curve to 1 hour (AUE0-1h) and 2 hours (AUE0-2h), Overall Drug Liking measured using VAS (at 12-h and 24-h post-dose in treatment phase), and Take Drug Again measured using VAS (at 12-h and 24-h post-dose in treatment phase). Despite of the abuse-deterrent properties of IDT-001 based on the comparison to crushed MS contin, IDT-001 has significantly higher VAS scores than placebo in most of above drug abuse measurements.

The assay sensitivity showed significant difference of crushed intranasal MS contin from placebo.

The results of the primary and some key secondary analyses on the completers set are summarized in Table 1.

Table 1. Summary of Paired-data Analysis for Primary and Some Key Secondary Endpoints–Completers population (N=25)

Endpoint	Crushed Intranasal IDT-001 60 mg	Crushed Intranasal MS Contin 60 mg	Intact IDT-001 60 mg	Placebo
Drug-Liking VAS (Emax)				
Mean (SE)	71.1 (2.6)	84.8 (2.6)	67.0 (2.6)	54.2 (2.6)
Drug - MS Contin (SE) 95% CI p-value	-13.7 (2.9) (-19.5, -7.8) <.0001		-17.7 (2.9) (-23.6, -11.9) *<.0001*	-30.6 (2.9) (-36.4, -24.7) <.0001
Drug – placebo (SE) 95% CI p-value	16.9 (2.9) (11.0, 22.8) <.0001		12.8 (2.9) (7.0, 18.7) <.0001	
Early Drug Liking (AUE_{0-1h})				
Mean (SEM)	54.4 (1.8)	63.0 (1.8)	49.8 (1.8)	49.6 (1.8)
Drug - MS Contin (SE) 95% CI p-value	-8.6 (2.4) (-13.3, -3.9) 0.0005		-13.1 (2.4) (-17.9, -8.4) *<.0001*	-13.5 (2.4) (-18.2, -8.7) <.0001
Drug – placebo (SE) 95% CI p-value	4.8 (2.4) (0.13, 9.6) 0.0442		0.3 (2.4) (-4.4, 5.0) 0.9042	
Early Drug Liking (AUE_{0-2h})				
Mean (SEM)	117.9 (3.9)	142.6 (3.9)	109.9 (3.9)	101.0 (3.9)
Drug - MS Contin (SE) 95% CI p-value	-24.6 (4.6) (-33.8, -15.5) <.0001		-32.7 (4.6) (-41.8, -23.5) *<.0001*	-41.5 (4.6) (-50.7, -32.4) <.0001
Drug – placebo (SE) 95% CI p-value	16.9 (4.6) (7.7, 26.1) 0.0005		8.9 (4.6) (-0.3, 18.0) 0.0567	
Take Drug Again VAS (E_{max})				
Mean (SEM)	66.6 (3.9)	76.6 (3.9)	64.3 (3.9)	49.5 (3.9)
Drug - MS Contin (SE) 95% CI p-value	-10.0 (4.6) (-19.1, -0.8) 0.0341		-12.2 (4.6) (-21.4, -3.0) *0.0103*	-27.0 (4.6) (-36.3, -17.8) <.0001
Drug – placebo (SE) 95% CI p-value	17.1 (4.6) (7.9, 26.3) 0.0004		14.9 (4.6) (5.7, 24.0) 0.0019	
Overall Drug-Liking VAS (E_{max})				
Mean (SEM)	67.0 (3.3)	77.3 (3.3)	65.6 (3.3)	51.7 (3.3)
Drug - MS Contin (SE) 95% CI p-value	-10.3 (3.7) (-17.7, -2.9) 0.0007		-11.7 (3.7) (-19.1, -4.3) *0.0025*	-25.5 (3.7) (-32.9, -18.1) <.0001
Drug – placebo (SE) 95% CI p-value	15.2 (3.7) (7.8, 22.6) 0.0001		13.9 (3.7) (6.5, 21.2) 0.0004	

Statistical considerations that may limit the effect:

- The missing rate of subjects from the study was 7%. The sponsor did not replace the 2 non-completers, leading to an unbalanced Williams square design in estimation of mean differences.
- In the sponsor proposed label Section 9.2, there were data of secondary endpoint take drug again which was not pre-specified for multiplicity adjustment in the SAP.
- The null hypothesis should be: the testing drug is not abuse-deterrent and the alternative hypothesis should be: the testing drug is abuse-deterrent.

Recommendations:

Recommendations for the proposed label are included in the subsection 2.2.2.2.

1 INTRODUCTION

1.1 Overview

1.1.1 Background Information

On 11/21/2014, the Agency received the submission of NDA206544 from Inspirion Delivery Technologies, LLC (the sponsor). The study M-ARER-002 included in this NDA submission needed a statistical review as requested by CSS on 12/12/2014. The sponsor submitted this study to request approval of Morphine ARER (Abuse Resistant Extended Release) (IDT-001), an abuse-deterrent formulation of morphine sulfate extended-release tablets, for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This drug formulation contains morphine (an opioid), a Schedule II controlled substance.

Study M-ARER-002 was entitled "A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, Four-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Doses of Crushed and Intact IDT-001 compared with Crushed MS Contin® and Placebo in Opioid Experienced, Non-Dependent Subjects Following Intranasal Administration"

1.1.2 Specific Studies Reviewed

The study M-ARER-002 is reviewed. The design properties are summarized in Table 2. Throughout this review, Crushed IDT-001 is referred to crushed Morphine ARER administered intranasally (intranasal route), Intact IDT-001 to intact oral Morphine ARER, Crushed MS Contin to crushed intranasal MS Contin (positive control), Placebo to crushed intranasal placebo.

Table 2. List of Studies Included in this Review

Study ID (Period)	Location	Design	Primary Endpoints	Treatments	Number of Subjects
M-ARER-002 (10/22/2012 – 1/3/2013)	1 site in Salt Lake City, UT	R, DB, AC, PC, SD, four-arms crossover to evaluate the abuse potential of single dose crushed and intact IDT-001	VAS Emax for Drug Liking	Crushed IDT-001 Intact IDT-001 Crushed MS Contin Placebo	27 randomized and 25 subjects completed all treatment periods

Abbreviations: DB = double blind; PC = placebo-controlled; AC = active-controlled; R = randomized; SD=single dose;

1.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA206544
Company	Inspirion Delivery Technologies, LLC
Drug	Morphine ARER
CDER EDR link	\\Cdsesub1\evsprod\NDA206544\0000
Letter date	November 21, 2014

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

In general, the data and analysis quality are acceptable.

2.2 Human Abuse Potential Study

2.2.1 Overview

2.2.1.1 Objectives of the Study

Primary Objective

The primary objective of this study was to determine the abuse potential of crushed and intact IDT-001 relative to crushed intranasal MS Contin® when administered intranasally and orally to non-dependent, recreational opioid users.

Secondary Objectives

- to determine the abuse potential of crushed and intact IDT-001 relative to placebo when administered intranasally to non-dependent, recreational opioid users;
- to determine the relative bioavailability of morphine in plasma from crushed and intact IDT-001 compared with crushed intranasal MS Contin when administered intranasally and orally to non-dependent, recreational opioid users; and

to determine the safety of crushed and intact IDT-001 compared with crushed intranasal MS Contin and placebo following intranasal and oral administration in non-dependent, recreational opioid users.

2.2.1.2 Study Design

This was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, four-way crossover, single-center study. The study consisted of a Screening Period, Qualification Period, Treatment Period and Follow-up Period.

The Screening Period was completed as an outpatient visit.

The Qualification Period consisted of a 3-night inpatient, double-blind qualifying session during which a Naloxone Challenge Test and Drug Discrimination Test were administered. Subjects who successfully passed the Naloxone Challenge Test and Drug Discrimination Test remained in

the clinic for a 48-hour washout period between and then entered the Treatment Period. Subjects were eligible for the Treatment Period, if they showed the following:

Drug Liking (bipolar VAS 0-100 mm scale)

- A minimum score (Emax) of 65 mm in response to active treatment in the first 2 hours following dosing.
- A ≥15 mm difference between active and placebo treatments in the first 2 hours following dosing.
- A placebo response ≥ 40 and ≤ 60 mm during the first 2 hours following dosing.

Drug High (unipolor VAS 0-100 mm scale)

- A ≥ 30 mm difference between active and placebo treatments during the first 2 hours following dosing.
- A placebo response ≥ 0 and ≤ 10 mm during the first 2 hours following dosing.

Additional criteria included:

- The ability to tolerate crushed 30 mg morphine sulfate IR administered intranasally as assessed by no emesis within 2 hours following dosing, ability to insufflate the entire volume of crushed treatments, or as otherwise as judged by the Investigator.
- Acceptable response to other study assessments, as determined by the Investigator.
- Ability to successfully complete the study as judged by the Investigator.

Treatment Period: Subjects received each of 4 treatments in a randomized, four-way crossover, double-blind, double-dummy, 1:1:1:1 ratio design. Each Treatment Period encompassed a 2-night stay for dosing, followed by a minimum 7-day outpatient washout period. During each treatment period subjects received a single treatment with 1 of the 4 study drugs:

- Treatment A: crushed intranasal IDT-00l placebo plus intact oral IDT-001 placebo (referred to as intranasal/oral placebo);
- Treatment B: crushed intranasal MS Contin 60 mg (with crushed Placebo Tablet for Reference Product added for volume) plus intact oral IDT-001 placebo (referred to as crushed intranasal MS Contin);
- Treatment C: crushed intranasal IDT-001 60 mg plus intact oral IDT-001 placebo (referred to as crushed intranasal IDT-001);
- Treatment D: crushed intranasal IDT-001 placebo plus intact oral IDT-001 60 mg (referred to as intact oral IDT-001).

Subjects were discharged from the clinical unit between each Treatment Period.

After completion of the Treatment Period, subjects returned in 7-10 days as an outpatient, to complete a 1-day Follow-up visit.

2.2.1.3 Abuse Potential Measures

PD endpoints for assessing abuse potential:

- Drug Liking measured using the Bipolar Visual Analog Scale (VAS) – primary parameter of interest.
- Drug Effects Questionnaire (DEQ; VAS for Any Drug Effects, Good Effects, Drug High, Bad Effects, Sick, Nausea, Sleepy and Dizzy)
- Snorting Experience measured using VAS
- Overall Drug Liking measured using VAS (at 12-h and 24-h post-dose in treatment phase)
- Take Drug Again measured using VAS (at 12-h and 24-h post-dose in treatment phase)
- Addiction Research Center Inventory (ARCI) / Morphine-Benzedrine Group (MBG) scale
- Pupillometry
- Price Value Assessment Questionnaire (PVAQ) (at 24-h post-dose in treatment phase)

Additional PD endpoints were also provided by the sponsor for Drug Liking, DEQ, and pupillometry:

- Peak effect (Emax)
- Time of peak effect (TEmax)
- Area under the effect curve to 1 hour (AUE0-1h)
- Area under the effect curve to 2 hours (AUE0-2h)
- Area under the effect curve to 8 hours (AUE0-8h)
- Area under the effect curve to 12 hours (AUE0-12h)
- Area under the effect curve to 24 hours (AUE0-24h)
- Area under the effect curve to time of observed maximum plasma morphine concentration (AUE0-Tmax).

Data collections were planned as seen in Table 3.

2.2.1.4 Analysis Population and Sample Size

Analysis populations

- Qualification Safety Population: Subjects who received at least one dose of study medication during the Qualification Period. This population was analyzed as treated.
- Safety Population: All randomized subjects who received at least one dose of study medication during the Treatment Period. This population was analyzed as treated.
- Pharmacodynamic (PD) Population: Subjects who completed all 4 treatment periods with at least 1 PD assessment in each treatment period. This was the primary population for PD analyses and was analyzed as randomized.
- Intent-to-Treat (ITT) Population: Subjects in the Safety population with at least 1 assessment during the Treatment Period. This was the secondary population for PD analyses and was analyzed as randomized.

Sample size estimate

Assuming an approximately 30% rate of dropout between the Qualification and Treatment Period, 42 subjects were to be enrolled to randomize 30 subjects and assuming an additional 20% dropout from the Treatment period it was estimated that 24 subjects would complete the study. With 24 subjects, this study was powered to detect a mean difference between Treatment C (crushed intranasal IDT-001) and Treatment B (crushed intranasal MS Contin) of 0.85 relative

effect size (mean to standard deviation ratio) with 80% power, assuming a two-sided alpha level of 0.05 and using SAS Proc Power, paired means test of differences and correlation of 0.

2.2.1.5 Statistical Methodologies used in the Sponsor's Analyses

Hypothesis testing:

For each of the parameters, the null hypothesis is: (b) (4), and the alternative hypothesis is: (b) (4).

(b) (4)

Statistical methodologies

The primary comparison was Treatment B (crushed intranasal MS Contin) vs. Treatment C (crushed intranasal IDT-001). All other comparisons were secondary. The comparison of Treatment B (crushed intranasal MS Contin) to Treatment A (intranasal/oral placebo) was made to confirm study validity.

The PD endpoints or applicable timepoints were analyzed using a mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% confidence intervals (CIs) were provided for each treatment. LS mean differences along with 95% CIs were provided for the pairwise treatment comparisons. Multiple comparison adjustments were made for the pairwise treatment comparisons of interest.

The sponsor also planned the following responders analysis. The percent reduction in peak effect (Emax) was calculated for Drug Liking. The percent reduction was calculated as:

$\%r\text{eduction} = (ci - ti) / (ci - pi) \times 100\%,\ i = 1, 2,\ldots, n$

where *ci*, *ti,* and *pi* are the Emax values for the control (Treatment B; crushed intranasal MS Contin), Test (Treatment C; crushed intranasal IDT-001), and the Placebo (Treatment A; intranasal/oral placebo), respectively; from the *i*th subject; and n is the sample size.

PD data were corrected for pre-dose (baseline adjusted) when pre-dose values were collected in accordance with the SAP. No additional adjustment for baseline measurements or any other covariate or prognostic factor was performed during the data analysis.

Handling of Dropouts or Missing Data

No algorithm for missing data imputation was employed except for where missing times for nonmissing PD parameters of interest were imputed as described in the SAP.

Multiple Comparisons/Multiplicity

The primary endpoint of interest, Emax, for the parameter of primary interest, Drug Liking, was tested at $\alpha = 0.05$ for the comparison between Crushed intranasal MS Contin and Crushed intranasal IDT-001 (Treatment B vs C). The comparisons between Crushed intranasal MS Contin

and Crushed intranasal IDT-001 for the endpoints AUE0-1h and AUE0-2h for Drug Liking were adjusted for multiplicity using the Benjamini-Hochberg method, setting the number of comparisons (m) equal to three, ie, adjusting for comparisons for AUE0-1h and AUE0-2h and the previous comparison for Emax. Additional pairwise comparisons for these variables will not be adjusted for multiplicity, as they are secondary to the primary efficacy hypothesis.

2.2.1.6 Changes in the Conduct of the Study

Sensitivity analyses were added that examined the distribution of the residuals from each parametric model for the PD analyses to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at α=0.01). If the residuals were not normally distributed, a $\log_e$ transformation was applied. If the $\log_e$ transformation was needed and the minimum value of the data was less than or equal to 0 a constant value was added to the data so that all values were greater than 1. In addition, homogeneity of variances was tested by allowing the model a different variance estimate for each treatment. This step was done after the residuals had been tested and if the $\log_e$ transformation was used, the transformed data were used in this test. If this model was preferable to the homogenous variance model (using the BIC-criteria smaller is better) then the heterogeneous variance model was used as the final model.

If the $\log_e$ transformation was used, the transformed LS means for each treatment and differences between treatments are presented for the transformed data and the back- transformed values, as appropriate.

The percent reduction analyses were also presented using the following equation in order to be consistent with future studies:

$$\%\,reduction = \left\{ \begin{array}{ll} \dfrac{c_i - t_i}{c_i - 50} \times \left(1 - \dfrac{p_i - 50}{50}\right) \times 100\%, & if\ p_i > 55; \\ \dfrac{c_i - t_i}{c_i - 50} \times 100\%, & if\ p_i \le 55. \end{array} \right\}, \quad i = 1, 2, ..., n$$

Profile plots of percent reduction were provided for each comparison and each of the three percent reduction formulas.

A post-hoc power analysis indicated, based on the variation observed for Morphine in the $AUC_{0\text{-}t}$ and C_{max} parameters, that a sample size of 27 subjects was sufficient to provide 91.1% power to show the test to reference ratio confidence interval for $\log_e$-transformed pharmacokinetic parameters within 80.00% and 125.00% bioequivalence criteria for a ratio within 5% of the reference, a coefficient of variation (CV) no greater than 30%, and an assumed correlation of 0.5.

2.2.1.7 Sponsor's Summary and Conclusions

Sponsor's results are attached in Appendix 1.

Sponsor's conclusion:

Study validity was confirmed with the comparison of LS Mean for E_{max} for Drug Liking being significantly higher for crushed intranasal MS Contin than crushed placebo (84.79 vs 54.22, $p < 0.0001$). The difference of LS Means between the crushed intranasal MS Contin and crushed

placebo were also statistically significantly higher ($p < 0.0001$) for $AUE_{0\text{-}1h}$, $AUE_{0\text{-}2h}$, $AUE_{0\text{-}8h}$, $AUE_{0\text{-}12h}$, and $AUE_{0\text{-}24h}$.

Table 11.4.9.2-1 presents an overall summary of statistical comparisons of PD parameters for Drug Liking. The LS means for Drug Liking were significantly lower for the crushed intranasal IDT-001 and intact oral IDT-001 than crushed intranasal MS Contin based on Emax and all AUE parameters, indicating that IDT-001 was less liked than MS Contin.

The differences of LS mean TE_{max} between IDT-001 and crushed intranasal MS Contin were not statistically significant.

No statistically significance in Drug Liking or TEmax was observed in LS mean difference between the intact and crushed intranasal IDT-001.

For percent reduction in E_{max}, 47% of subjects preferred intact oral IDT-001, 33% of subjects preferred crushed intranasal IDT-001, and 19% of subjects had no preference. These results suggest a similar abuse profile.

Table 11.4.9.2-1: Overall Summary of Statistical Comparisons of PD Parameters for the Primary Endpoint, Drug Liking (PD Population, N = 25)

	LS Mean Difference						% Subjects
	E_{max}	$AUE_{0\text{-}1h}$	$AUE_{0\text{-}2h}$	$AUE_{0\text{-}8h}$	$AUE_{0\text{-}24h}$	TE_{max}	Reduction in E_{max}
Crushed MS Contin vs Crushed IDT-001[a]	13.65[c]	8.60[d]	24.64[c]	48.16[d]	81.70[d]	-0.49[e]	76%
Intact IDT-001 vs Crushed IDT-001[b]	-4.11[e]	-4.56[e]	-8.03[e]	-30.51[e]	-43.36[e]	0.08[e]	33%
Crushed MS Contin vs Intact IDT-001[a]	17.76[c]	13.17[c]	32.67[c]	78.67[d]	125.06[d]	-0.57[e]	84%

[a]Positive values for E_{max} and AUE indicate less drug liking for crushed and intact oral IDT-001 vs MS Contin; negative values for TE_{max} indicate longer period of time to reach peak effect with crushed and intact IDT-00l vs MS Contin; 76% and 84% of subjects had a reduction in E_{max} with crushed or intact oral IDT-001 vs MS Contin, respectively.
[b]Negative values for E_{max} and AUE indicate less drug liking for intact oral IDT-001compared with crushed intranasal IDT-001; positive value for TE_{max} 33% of subjects had a reduction in E_{max} with crushed intranasal IDT-001 compared with intact oral IDT-001.
[c]$p \leq 0.0001$
[d]$p \leq 0.05$
[e]not significant
Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.9.2-1.

2.2.2 Reviewer's Assessment

2.2.2.1 REVIEWER's ANALYSES

This reviewer checked the normality assumption of the analysis model and verified the sponsor's primary and some secondary analyses.

In addition, the first-order carryover effect is not significant and does not need to be included in the analysis model.

This reviewer verified the sponsor's analyses on the primary and key secondary endpoints, including drug-liking (at the moment) VAS-E_{max}, AUE_{-1h} and AUE_{-2h}, and take drug again VAS-E_{max}.

Responder analysis showed that the percentage of subjects with response rate ≥30% relative to crushed MS contin was not significant from 50% of the total subjects. The plot of subject's percentage versus responder percentage is shown in Appendix 2.

This reviewer provided a descriptive summary of the PD measures for drug abuse in Appendix 2.

2.2.2.2 Conclusion

2.2.2.2.1 Statistical Issues

- The missing rate of subjects from the study was 7%. The sponsor did not replace the 2 non-completers, leading to an unbalanced Williams square design in estimation of mean differences.
- In the sponsor proposed label Section 9.2, there were data of secondary endpoint take drug again which was not pre-specified for multiplicity adjustment in the SAP.
- The null hypothesis should be: the testing drug is not abuse-deterrent and the alternative hypothesis should be: the testing drug is abuse-deterrent.

2.2.2.2.2 Conclusions and Recommendations

The numbers of completers were 25 (93%) with a total of 27 subjects randomized to the treatment phase. The number of completers assured the analysis power greater than 80% for detecting a significant difference between crushed intranasal IDT-001 and crushed intranasal MS Contin with 80% power under the sample size assumptions at a two-sided alpha level of 0.05 on the Drug Liking (at the moment) VAS.

This reviewer confirmed the sponsor's results about the abuse-deterrent properties of crushed intranasal and intact oral IDT-001 relative to the positive control, crushed intranasal MS contin, based on the pre-defined primary and secondary endpoints: Drug Liking (at the moment) VAS, areas under the Drug Liking curve to 1 hour (AUE0-1h) and 2 hours (AUE0-2h), Overall Drug Liking measured using VAS (at 12-h and 24-h post-dose in treatment phase), and Take Drug Again measured using VAS (at 12-h and 24-h post-dose in treatment phase). Despite of the abuse-deterrent properties of IDT-001 based on the comparison to crushed MS contin, IDT-001 has significantly higher VAS scores than placebo in most of above drug abuse measurements.

The assay sensitivity showed significant difference of crushed intranasal MS contin from placebo.

2.2.2.2.3 Labeling Recommendations

The statistical review addresses statements in the label (section 9: DRUG ABUSE AND DEPENDENCE) concerning:

1. In *Clinical Abuse Potential Studies* of Section 9.2, on p17 the last paragraph:

"A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in (b) (4) non-dependent recreational opioid users with a history of intranasal drug abuse was performed to determine the relative bioavailability and abuse potential of crushed intranasal **BRAND NAME** 60 mg tablets compared with crushed intranasal (b) (4) (b) (4) 60 mg tablets, and intact orally administered **BRAND NAME** 60 mg tablets. The intact oral tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route. (b) (4) ,,

2. The AUEs results on Table (b) (4) in Section 9 are expressed as (b) (4) which are numerically diffe nt from Table 11.4.9.2-1 in sponsor's report-body.pdf (the later were verified by this reviewer). Please explain how the adjustments were made, otherwise use the results in the report-body.
3. On Table (b) (4) there were data of secondary endpoint take drug again which was not pre-specified for multiplicity adjustment in the SAP. This result should be in the text and clearly m ked as "Not adjusted for multiplicity".
4. On Table (b) (4) it is not clear how the sponsor computed the data in the category "Crushed Intranasal (b) (4) vs. Crushed Intranasal BRAND NAME (b) (4)". The sponsor should explain this and its meaning. (Internal question to CSS - is this information necessary to be included in the label?)
5. The first paragraph on page 20,

(b) (4) experienced some reduction in E_{max} of Drug Liking VAS with crushed (b) (4) **BRAND NAME** compared with crushed (b) (4) extended-release morphine, 48%; (n =12) experienced at least a 30% reduction in E_{max} and (b) (4)% (n = (b) (4), experienced at least a (b) (4)% reduction in E_{max} of drug liking (b) (4)

(b) (4)


(b) (4)

3 APPENDIX

3.1 Appendix 1

Table 3: Schedule of Events

Assessments	Screening	Qualification Period				Treatment Period 1			Treatment Periods 2, 3,4 (End of Study)				Follow-up/ ET
		Check-in Day -1	Dose Day 1	Dose Day 2	Wash out	Dose Day 1	Discharge	Washout	Check-in	Dose Day 2-4	Discharge	Washout	
Visit	**1**	**2**							**3, 4,5**				**6**
Informed Consent	X												
Inclusion / Exclusion	X	X[1]							X[1]				
Demographics	X												
Medical History	X	X[2]							X[2]				X[2]
Alcohol and Drug Use History	X												
Physical Exam	X	X[3]					X[3]		X[3]		X[3]		X
12-lead ECG	X	X											X
Continuous Oxygen Saturation Monitoring[4]			X	X		X				X			
Continuous 3-lead telemetry[5]						X				X			
Vital Signs[6]	X	X	X	X		X			X	X			X
Serology	X												
Clinical Lab Tests[7]	X	X											X
Urine Drug Screen / Ethanol Breath Test[8]	X	X							X				
Pregnancy Test[9]	X	X							X				X
Naloxone Challenge Test		X											
PD Questionnaire Training[10]		X											
Randomization			X			X							
Drug Dosing[11]			X	X		X				X			
PK Samples[12]						X				X			
ARCI / MBG[13]			X	X		X				X			
Drug Liking VAS[14]			X	X		X				X			
DEQ VAS[15]			X	X		X				X			
Overall Drug Liking, Take Drug Again VAS, and Price Value Assessment Questionnaire[16]			X	X		X				X			
Pupillometry[17]						X				X			
Snorting Experience VAS[18]			X	X		X				X			
Adverse Events[19]		X	X	X		X	X		X	X	X		X
Concomitant Medications[20]	X	X	X	X		X	X		X	X	X		X

ET = Early Termination

1. Inclusion/Exclusion: after the Screening visit, inclusion/exclusion criteria were reviewed at the Qualification Check-in and at each Treatment Period check-in to assess continued eligibility of the subject.
2. Medical History: updated at subsequent visits after the Screening Period.
3. Physical Exam: complete physical exam at Screening and Follow-up/Early Termination; abbreviated physical exams at check-in and discharge during the Qualification & Treatment Periods could be performed if there was a change in medical status (at discretion of Investigator); physical exam at Screening included height and weight;

physical exam at Follow-up included weight.
4. Continuous oxygen saturation monitoring: subjects were on continuous oxygen monitoring beginning pre-dose to 8 h postdose on dosing days.
5. Continuous 3-lead heart monitoring: beginning pre-dose to 8 h postdose on dosing days in the Treatment Period.
Source: sponsor's study m-arer-002 report-body.pdf Table 9.5.1-1.

Table 4. Patient disposition (Randomized Set)

Study Population	Overall
Qualification Safety Population	48
Safety Population	27
Pharmacodynamic (PD) Population	25
Intent-to-Treat (ITT) Population	27
Pharmacokinetic Population	27

Source: sponsor's study m-arer-002 report-body.pdf Table 11.1-1.

Of the 48 subjects who entered the study, 38 (79%) had at least 1 protocol deviation (Listing 16.2.2-1). Table 10.2-1: Protocol Deviations (All Subjects) lists subjects who experienced a protocol deviation. The most common deviations were assessments taken outside of the ±10 minute window (n = 20), assessment not performed (n = 19), and assessment time not recorded (n = 16). None of the deviations were considered major.

Table 5: Overall Summary of Statistical Comparisons of PD Parameters for the Primary Endpoint, Drug Liking (PD Population, N = 25)

	LS Mean Difference						% Subjects
	E_{max}	AUE_{0-1h}	AUE_{0-2h}	AUE_{0-8h}	AUE_{0-24h}	TE_{max}	Reduction in E_{max}
Crushed MS Contin vs Crushed IDT-001[a]	13.65[c]	8.60[d]	24.64[c]	48.16[d]	81.70[d]	-0.49[e]	76%
Intact IDT-001 vs Crushed IDT-001[b]	-4.11[e]	-4.56[e]	-8.03[e]	-30.51[e]	-43.36[e]	0.08[e]	33%
Crushed MS Contin vs Intact IDT-001[a]	17.76[c]	13.17[c]	32.67[c]	78.67[d]	125.06[d]	-0.57[e]	84%

[a]Positive values for E_{max} and AUE indicate less drug liking for crushed and intact oral IDT-001 vs MS Contin; negative values for TE_{max} indicate longer period of time to reach peak effect with crushed and intact IDT-00l vs MS Contin; 76% and 84% of subjects had a reduction in E_{max} with crushed or intact oral IDT-001 vs MS Contin, respectively.
[b]Negative values for E_{max} and AUE indicate less drug liking for intact oral IDT-001compared with crushed intranasal IDT-001; positive value for TE_{max} 33% of subjects had a reduction in E_{max} with crushed intranasal IDT-001 compared with intact oral IDT-001.
[c]$p \leq 0.0001$
[d]$p \leq 0.05$
[e]not significant
Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.9.2-1.

Table 6: Statistical Analyses of Emax for Take Drug Again Assessment (PD Population, N = 25)

Parameter	Crushed MS Contin vs Crushed IDT-001	Intact IDT-001 vs Crushed IDT-001	Crushed MS Contin vs Intact IDT-001
E_{max} (mm)			
LS mean difference	9.96	-2.23	12.19
95% CI of the difference	0.77, 19.14	-11.45, 6.98	2.97, 21.40
Unadjusted p-value	0.0341	0.6306	0.0103

Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.2.10-1.

Table 7: Statistical Analyses of Emax for Overall Drug Liking VAS (PD Population, N = 25)

Parameter	Crushed MS Contin vs Crushed IDT-001	Intact IDT-001 vs Crushed IDT-001	Crushed MS Contin vs Intact IDT-001
E_{max} (mm)			
LS mean difference	10.29	-1.38 (3.712)	11.66 (3.712)
95% CI of the difference	2.91, 17.67	-8.78, 6.03	4.26, 19.07
Unadjusted p-value	0.0070	0.7120	0.0025

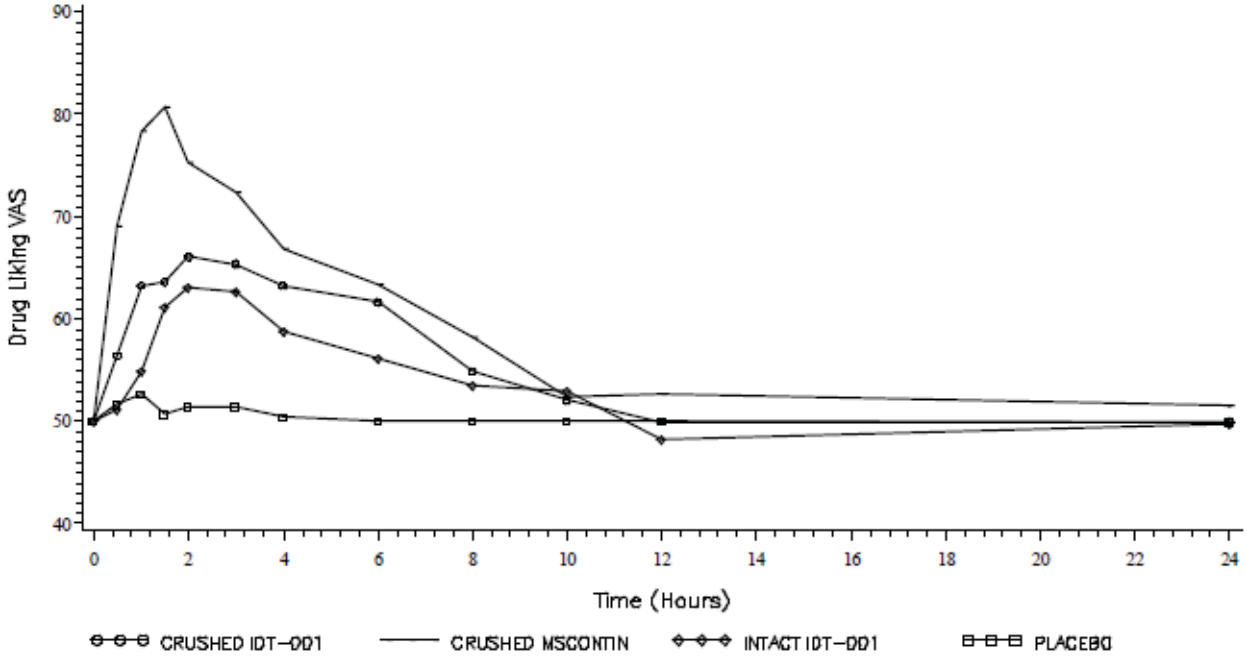
Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.2.9-1.

Table 8: Statistical Analyses of the Price Value Assessment Questionnaire (PD Population, N = 25)

Parameter	Crushed MS Contin vs Crushed IDT-001	Intact IDT-001 vs Crushed IDT-001	Crushed MS Contin vs Intact IDT-001
Price Value at 24 Hours			
LS mean difference	2.03	-0.31	2.34
95% CI of the difference	0.69, 3.36	-1.65, 1.02	1.00, 3.68
Unadjusted p-value	0.0034	0.6409	0.0008

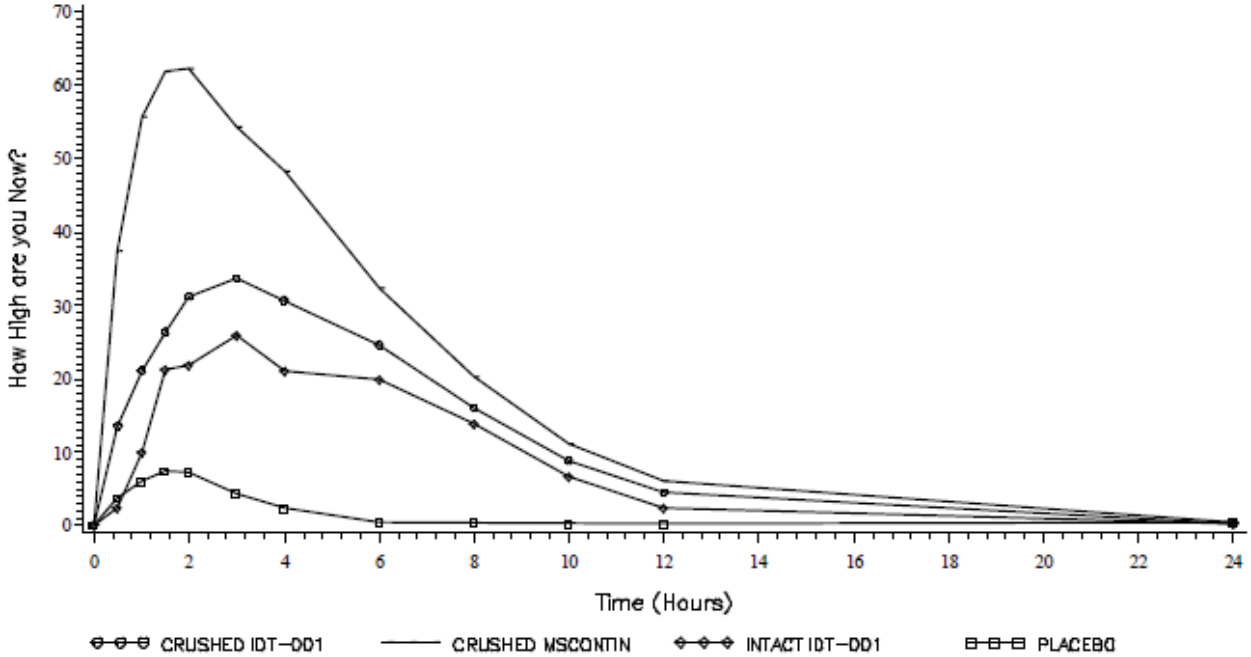
Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.2.12-1.

Figure 1 Mean Scores Over Time for "At This Moment" Drug Liking VAS (PD Population, N = 25)



Source: sponsor's study m-arer-002 report-body.pdf Figure 11.4.2.3-1.

Figure 2: Mean "Drug High" Over Time (PD Population, N = 25)



Source: sponsor's study m-arer-002 report-body.pdf Figure 11.4.2.7.3-1.

Secondary Analysis

Table 9 Overall Summary of LS Mean Comparisons for Emax for Secondary Endpoints (PD Population, N = 25)

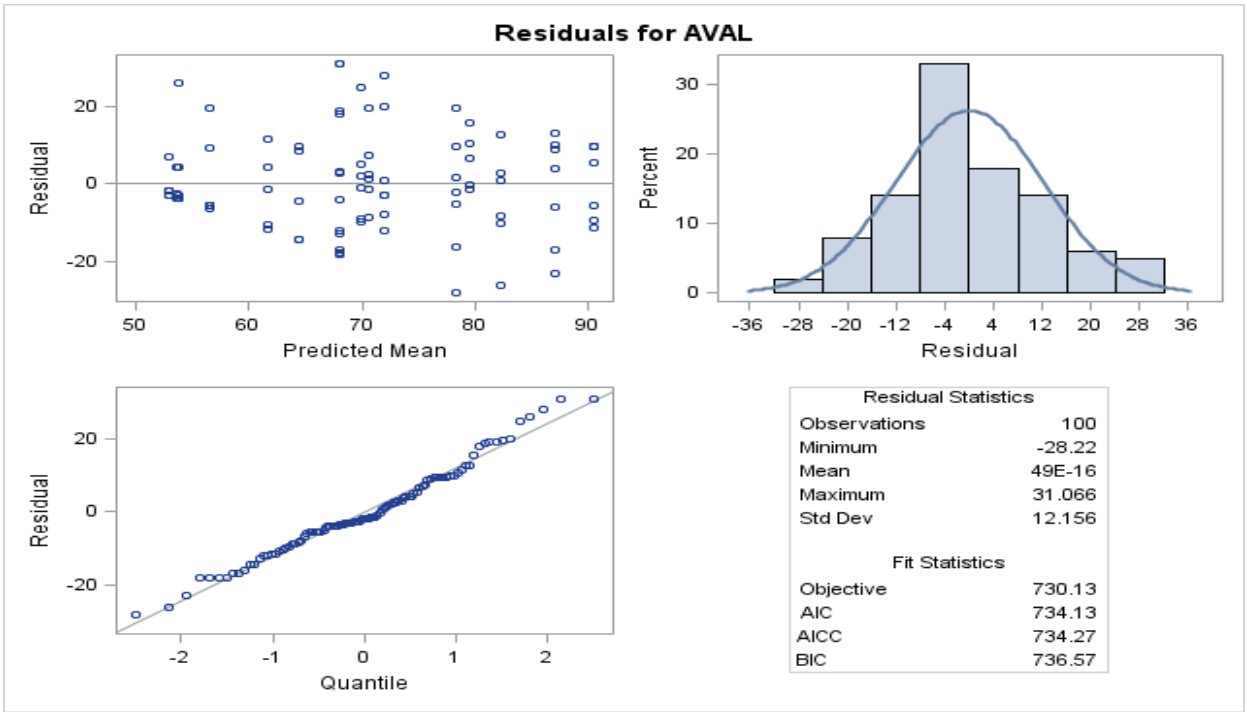
	Crushed MS Contin vs Crushed IDT-001	Intact IDT-001 vs Crushed IDT-001	Crushed MS Contin vs Intact IDT-001
Drug Effects Questionnaire			
Any Effects	68.2 v 44.8, p=0.0003	33.7 v 44.8, p=0.0744	68.2 v 33.7, p<0.0001
Good Effects	69.5 v 45.6, p=0.0004	32.9 v 45.6, p=0.0526	69.5 v 32.9, p<0.0001
Drug High	67.7 v 43.0, p=0.0001	34.2 v 43.0, p=0.1499	67.7 v 34.2, p<0.0001
Bad Effects	19.4 v 12.6, p=0.0951	11.1 v 12.6, p=0.7183	19.4 v 11.1, p=0.0443
Sick	18.4 v 8.5, p=0.0141	14.1 v 8.5, p=0.1595	18.4 v 14.1, p=0.2807
Nausea	20.4 v 10.5, p=0.0141	14.2 v 10.5, p=0.3554	20.4 v 14.2, p=0.1186
Sleepy	31.8 v 25.6, p=0.2251	17.2 v 25.6, p=0.1024	31.8 v 17.2, p=0.0054
Dizzy	11.8 v 8.0, p=0.1136	8.5 v 8.0, p=0.8455	11.8 v 8.5, p=0.1654
Overall Drug Liking	77.3 v 67.0, p=0.0070	65.6 v 67.0, p=0.7120	77.3 v 65.6, p=0.0025
Take Drug Again Assessment	76.5 v 66.6, p=0.0341	64.3 v 66.6, p=0.6306	76.5 v 64.3, p=0.0103
ARCI/MBG	10.6 v 8.5, p=0.0511	6.6 v 8.5, p=0.0780	10.6 v 6.6, p=0.0003
Pupillometry	2.6 v 2.4, p=0.1619	2.1 v 2.4, p=0.1813	2.6 v 2.1, p=0.0074

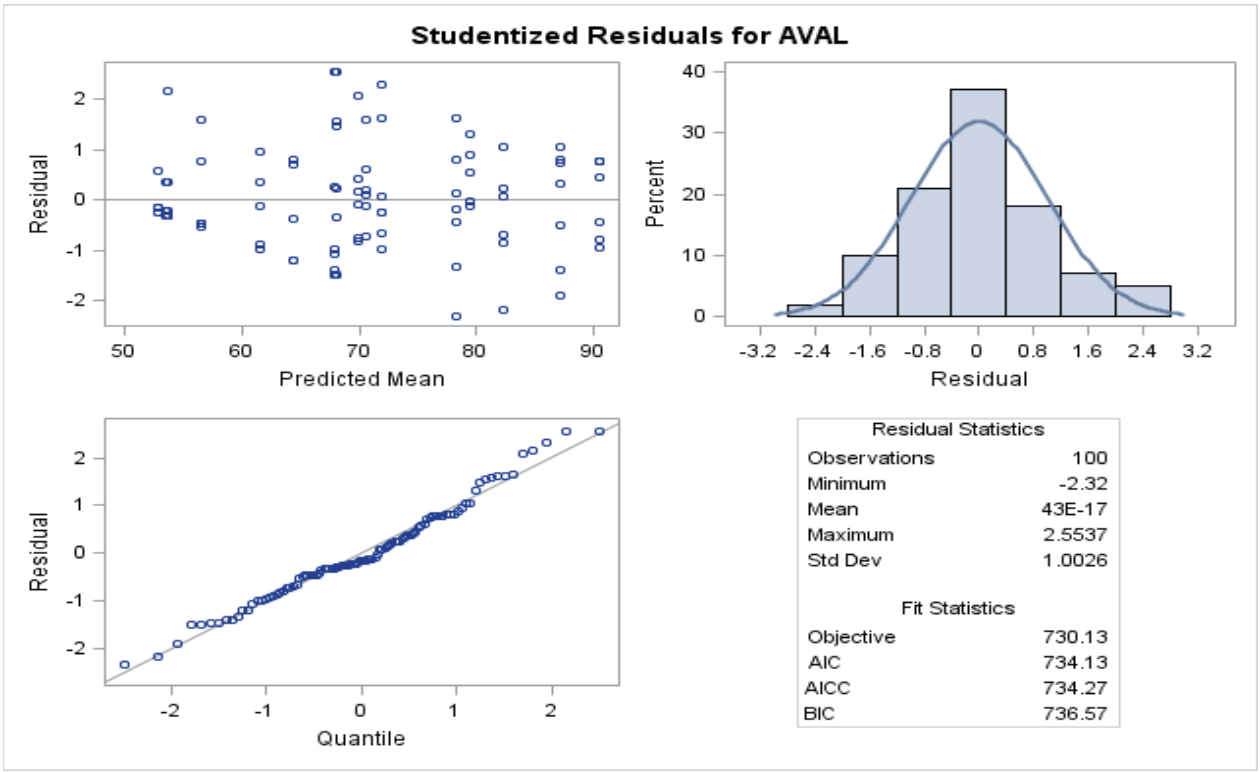
Source: sponsor's study m-arer-002 report-body.pdf Table 11.4.9.2-2

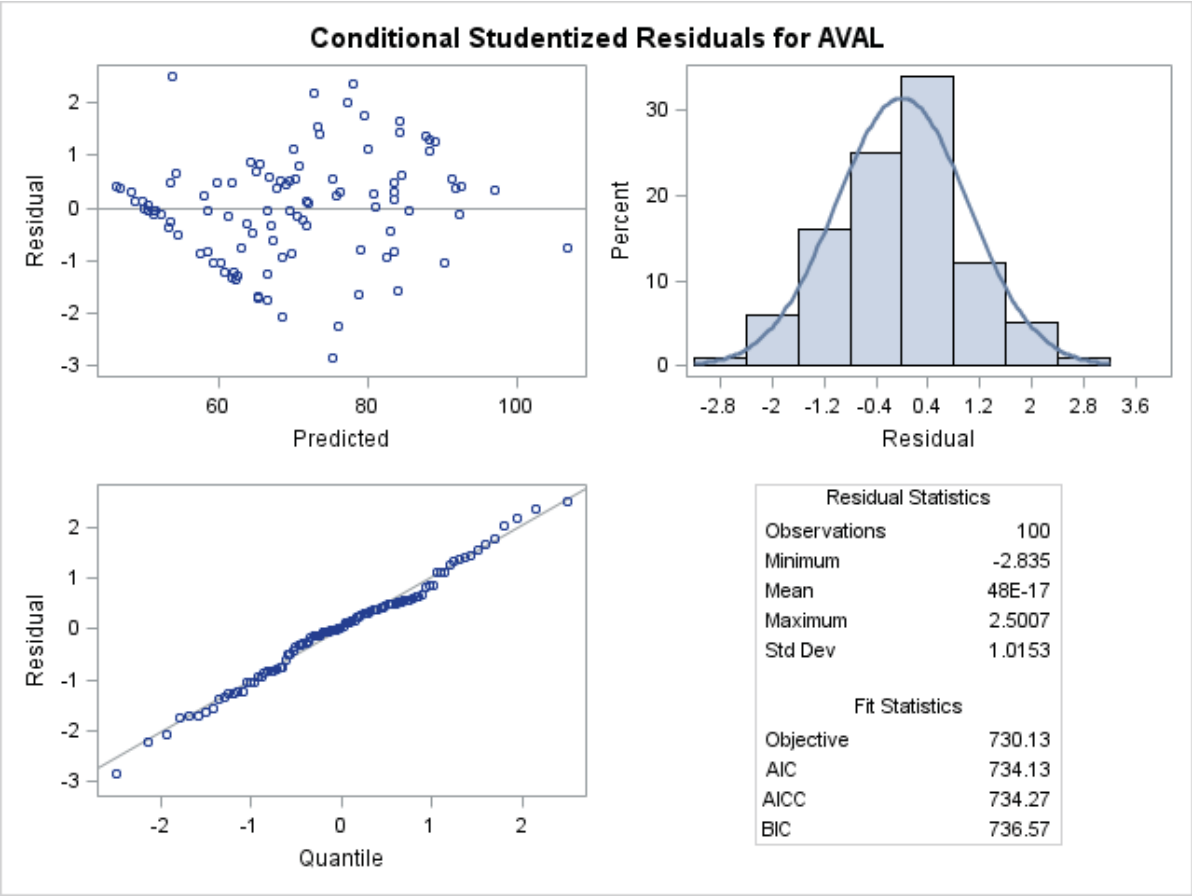
(b) (4)

3.2 Appendix 2

Figure 4 Normality assumption of the analysis model






Conditional Studentized Residuals for AVAL
Residual
Predicted
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 100
Minimum -2.835
Mean 48E-17
Maximum 2.5007
Std Dev 1.0153
Fit Statistics
Objective 730.13
AIC 734.13
AICC 734.27
BIC 736.57

(b) (4)

Figure 11 Summary of Paired-data Analysis for Primary and Some Key Secondary Endpoints–Completers population (N=25)

Endpoint	Crushed Intranasal IDT-001 60 mg	Crushed Intranasal MS Contin 60 mg	Intact IDT-001 60 mg	Placebo
Drug-Liking VAS (Emax)				
Mean (SE)	71.1 (2.6)	84.8 (2.6)	67.0 (2.6)	54.2 (2.6)
Drug - MS Contin (SE) 95% CI p-value	-13.7 (2.9) (-19.5, -7.8) <.0001		-17.7 (2.9) (-23.6, -11.9) *<.0001*	-30.6 (2.9) (-36.4, -24.7) <.0001
Drug – placebo (SE) 95% CI p-value	16.9 (2.9) (11.0, 22.8) <.0001		12.8 (2.9) (7.0, 18.7) <.0001	
Early Drug Liking (AUE_{0-1h})				
Mean (SEM)	54.4 (1.8)	63.0 (1.8)	49.8 (1.8)	49.6 (1.8)
Drug - MS Contin (SE) 95% CI p-value	-8.6 (2.4) (-13.3, -3.9) 0.0005		-13.1 (2.4) (-17.9, -8.4) *<.0001*	-13.5 (2.4) (-18.2, -8.7) <.0001
Drug – placebo (SE) 95% CI p-value	4.8 (2.4) (0.13, 9.6) 0.0442		0.3 (2.4) (-4.4, 5.0) 0.9042	
Early Drug Liking (AUE_{0-2h})				
Mean (SEM)	117.9 (3.9)	142.6 (3.9)	109.9 (3.9)	101.0 (3.9)
Drug - MS Contin (SE) 95% CI p-value	-24.6 (4.6) (-33.8, -15.5) <.0001		-32.7 (4.6) (-41.8, -23.5) *<.0001*	-41.5 (4.6) (-50.7, -32.4) <.0001
Drug – placebo (SE) 95% CI p-value	16.9 (4.6) (7.7, 26.1) 0.0005		8.9 (4.6) (-0.3, 18.0) 0.0567	
Take Drug Again VAS (E_{max})				
Mean (SEM)	66.6 (3.9)	76.6 (3.9)	64.3 (3.9)	49.5 (3.9)
Drug - MS Contin (SE) 95% CI p-value	-10.0 (4.6) (-19.1, -0.8) 0.0341		-12.2 (4.6) (-21.4, -3.0) *0.0103*	-27.0 (4.6) (-36.3, -17.8) <.0001
Drug – placebo (SE) 95% CI p-value	17.1 (4.6) (7.9, 26.3) 0.0004		14.9 (4.6) (5.7, 24.0) 0.0019	
Overall Drug-Liking VAS (E_{max})				
Mean (SEM)	67.0 (3.3)	77.3 (3.3)	65.6 (3.3)	51.7 (3.3)
Drug - MS Contin (SE) 95% CI p-value	-10.3 (3.7) (-17.7, -2.9) 0.0007		-11.7 (3.7) (-19.1, -4.3) *0.0025*	-25.5 (3.7) (-32.9, -18.1) <.0001
Drug – placebo (SE) 95% CI p-value	15.2 (3.7) (7.8, 22.6) 0.0001		13.9 (3.7) (6.5, 21.2) 0.0004	

Responder's analysis

Figure 12 "At This Moment" Drug Liking VAS Emax Responder Analysis, IDT-001 vs Crushed MS Contin, Per Protocol Population

	Percent Reduction		
	≥30%	≥40%	≥50%
Crushed intranasal IDT-001			
Responder rate	0.48	0.36	na
Z-score	-2.08	-1.45	
P value	0.582	0.927	
Intact oral IDT-001			
Responder rate	0.60	0.48	0.40
Z-score	1.04	-2.08	-1.04
P value	0.149	0.582	0.85

(b) (4)

Figure 13 Summary of endpoint measures for drug abuse (Completers Set)

Endpoint	treatment	n	mean	stderr	min	Q1	median	Q3	max
Drug Liking AUE [0-12h]	CRUSHED IDT-001	25	697.44	20.22	597.33	618.33	667.10	764.79	933.20
	CRUSHED MSCONTIN	25	752.57	29.28	520.78	667.13	737.04	816.76	1108.23
	INTACT IDT-001	25	666.52	20.33	557.25	600.00	656.50	697.33	1061.83
	PLACEBO	25	604.85	4.42	575.83	598.00	598.48	603.25	698.85
Drug Liking AUE [0-1h]	CRUSHED IDT-001	25	54.75	1.74	47.50	48.33	52.50	57.92	85.00
	CRUSHED MSCONTIN	25	63.25	2.94	36.53	51.83	59.88	77.83	84.52
	INTACT IDT-001	25	49.88	0.63	47.50	48.33	48.58	50.33	62.73
	PLACEBO	25	49.60	0.81	41.93	47.98	48.33	48.82	61.60
Drug Liking AUE [0-24h]	CRUSHED IDT-001	25	1298.48	21.42	1186.06	1218.33	1267.10	1381.17	1533.20
	CRUSHED MSCONTIN	25	1380.37	44.20	1120.78	1267.13	1345.47	1419.98	2230.23
	INTACT IDT-001	25	1254.98	26.45	856.17	1198.33	1250.50	1304.18	1661.83
	PLACEBO	25	1204.27	4.68	1175.83	1196.50	1198.33	1206.70	1304.85
Drug Liking AUE [0-2h]	CRUSHED IDT-001	25	118.63	4.37	97.50	100.33	116.08	125.43	185.00
	CRUSHED MSCONTIN	25	143.10	5.26	88.53	127.08	140.88	164.38	183.27
	INTACT IDT-001	25	110.01	2.46	97.50	98.33	111.58	115.83	134.83
	PLACEBO	25	101.02	2.33	75.83	97.83	98.33	98.83	134.85
Drug Liking AUE [0-8h]	CRUSHED IDT-001	25	490.30	17.99	397.33	418.33	467.10	546.30	697.20
	CRUSHED MSCONTIN	25	538.70	22.22	364.78	467.13	528.63	582.02	783.24
	INTACT IDT-001	25	458.35	14.61	371.58	398.50	455.68	489.33	721.83
	PLACEBO	25	404.19	4.38	375.83	397.35	398.33	401.58	497.85
Drug Liking AUE [0-Tmax]	CRUSHED IDT-001	25	96.09	8.78	48.33	72.23	86.43	100.33	208.67
	CRUSHED MSCONTIN	25	60.17	5.70	17.78	35.75	57.43	77.72	134.02
	INTACT IDT-001	25	95.61	9.04	23.33	72.50	82.78	118.75	191.23
	PLACEBO	25	50.00	0.00	50.00	50.00	50.00	50.00	50.00
Drug Liking Emax	CRUSHED IDT-001	25	71.72	2.87	50.00	61.00	72.00	76.00	100.00
	CRUSHED MSCONTIN	25	85.32	2.42	56.00	79.00	85.00	96.00	100.00
	INTACT IDT-001	25	67.32	3.13	50.00	51.00	66.00	73.00	99.00
	PLACEBO	25	54.32	1.63	50.00	50.00	51.00	51.00	80.00
Drug Liking TEmax	CRUSHED IDT-001	25	2.32	0.34	0.45	0.97	1.97	2.97	5.97
	CRUSHED MSCONTIN	25	1.82	0.26	0.45	0.97	1.47	1.97	5.95
	INTACT IDT-001	25	2.42	0.31	0.45	1.47	1.97	2.97	5.95
	PLACEBO	25	1.68	0.46	0.45	0.47	0.95	1.48	9.97
	CRUSHED IDT-001	25	67.08	3.28	44.00	50.00	67.00	76.00	100.00
	CRUSHED MSCONTIN	25	77.40	3.78	16.00	72.00	80.00	87.00	100.00
	INTACT IDT-001	25	65.52	3.88	13.00	50.00	67.00	74.00	100.00
	PLACEBO	25	51.48	0.91	43.00	50.00	50.00	50.00	63.00
Overall Drug Liking	CRUSHED IDT-001	25	66.44	3.76	38.00	50.00	64.00	79.00	100.00
	CRUSHED MSCONTIN	25	76.40	4.17	17.00	70.00	75.00	98.00	100.00
	INTACT IDT-001	25	64.04	4.58	0.00	50.00	60.00	82.00	100.00
	PLACEBO	25	49.08	2.21	0.00	50.00	50.00	50.00	64.00
	CRUSHED IDT-001	25	697.44	20.22	597.33	618.33	667.10	764.79	933.20
	CRUSHED MSCONTIN	25	752.57	29.28	520.78	667.13	737.04	816.76	1108.23
	INTACT IDT-001	25	666.52	20.33	557.25	600.00	656.50	697.33	1061.83
Take Drug Again	PLACEBO	25	604.85	4.42	575.83	598.00	598.48	603.25	698.85
	CRUSHED IDT-001	25	54.75	1.74	47.50	48.33	52.50	57.92	85.00
	CRUSHED MSCONTIN	25	63.25	2.94	36.53	51.83	59.88	77.83	84.52
	INTACT IDT-001	25	49.88	0.63	47.50	48.33	48.58	50.33	62.73
	PLACEBO	25	49.60	0.81	41.93	47.98	48.33	48.82	61.60
	CRUSHED IDT-001	25	1298.48	21.42	1186.06	1218.33	1267.10	1381.17	1533.20
	CRUSHED MSCONTIN	25	1380.37	44.20	1120.78	1267.13	1345.47	1419.98	2230.23

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