# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205525Orig1s000

# 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 205-525/0003 |
| **Supplement Number:** | NA |
| **Drug Name:** | Dronabinol oral solution |
| **Indication(s):** | Human abuse liability |
| **Applicant:** | Insys Therapeutics, Inc. |
| **Date(s):** | Date of Document: 6/1/2015<br>Consult received date: 10/18/2015<br>Completion date: 12/18/2015 |
| **Review Priority:** | P (45 days) |
| **Biometrics Division:** | Division of Biometrics VI |
| **Statistical Reviewer:** | Wei Liu, Ph.D., Mathematical Statistician, QT-CSS/DBVI/OB/OTS |
| **Concurring Reviewers:** | Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS<br>Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS |
| **Medical Division:** | Controlled Substance Staff |
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| **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 NDA205525 (IND 075228) were submitted by Inspirion Delivery Technologies, LLC (the sponsor) for requesting approval of dronabinol oral solution for the management of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy. The study INS-13-017 included in this NDA needed a statistical review for drug abuse liability.

Confirmation of abuse-potential:
Study INS-13-017 was a phase 1, two-dose, randomized, double-blind, double-dummy, placebo- and active-controlled to determine the abuse potential of dronabinol oral solution compared with Marinol (NDA 018651 dronabinol capsules, approved 5/31/1985) and placebo in recreational cannabinoid users.

There were a total of 43 subjects randomized to the Treatment phase after a Qualification phase. The numbers of completers who completed all treatment sessions and had no major protocol deviations were 33 (77%). Ten subjects discontinued in the Treatment phase, 5 of them withdrew after receiving 30 mg Dronabinol Oral Solution while 3 after taking 30 mg Marinol.

The descriptive analysis of the primary and some key secondary endpoints (peak VAS of Overall drug liking, Take drug Again, and High) by this reviewer are the same as those by the sponsor. This reviewer confirmed the sponsor's results about the abuse liability of Dronabinol Oral Solution (10 mg and 30 mg) using the positive control Marinol (10 mg and 30 mg), based on the pre-defined primary and key secondary endpoints: peak effects of Drug Liking (at the moment) and HighVAS, and areas under VAS curves during the treatment period, 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). The differences between Marinol and Dronabinol Oral Solution at either high (30 mg) or low dose (10 mg) are not statistically significant in the primary and key secondary PD endpoints. However, the endpoint values of Dronabinol Oral Solution 30 mg are numerically larger than that of Marinol 30 mg. The similar observations are also seen at the dose of 10 mg except for the endpoints Take Drug Again and Overall Drug Liking.

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

Statistical considerations that may limit the effect:

- The null hypotheses were not defined for both the primary analysis and the analysis of secondary PD endpoints.
- There were a total of 10 subjects discontinued before the end of Treatment phase and 5 of them were after receiving 30 mg Dronabinol Oral Solution while 3 after taking 30 mg Marinol. The sponsor did not replace these non-completers, leading to an unbalanced Williams square design in estimation of mean differences.

Recommendations:
Recommendations for the proposed label are included in the subsection 2.2.2.3.2.

## Table I. Results of Wilcoxon Rank Sum Test on Completers Paired-data for Primary and Some Key Secondary Endpoints (N=33)

| PARAM | endpoint | diff | mean | STDERR | Q3 | Median | Q1 | pSignRank |
|---|---|---|---|---|---|---|---|---|
| Drug Liking VAS | Emax | D - B | 2.67 | 2.09 | 4 | 0 | 0 | 0.1071 |
| Drug Liking VAS | Emax | C - A | 3.24 | 2.53 | 10 | 0 | -3 | 0.3398 |
| Drug Liking VAS | Emax | A - E | 23.88 | 4.14 | 49 | 24 | 8 | <0.0001 |
| Drug Liking VAS | Emax | B - E | 34.79 | 2.77 | 49 | 38 | 25 | <0.0001 |
| Drug Liking VAS | Emax | C - E | 27.12 | 3.05 | 45 | 27 | 11 | <0.0001 |
| Drug Liking VAS | Emax | D - E | 37.45 | 2.69 | 50 | 43 | 32 | <0.0001 |
| Drug Liking VAS | TA_AUE | D - B | 0.30 | 1.44 | 2.60 | -0.03 | -2.49 | 0.9235 |
| Drug Liking VAS | TA_AUE | C - A | 0.03 | 2.24 | 1.36 | -0.21 | -1.13 | 0.7841 |
| Drug Liking VAS | TA_AUE | A - E | 5.92 | 1.80 | 5.86 | 3.05 | 0.93 | <0.0001 |
| Drug Liking VAS | TA_AUE | B - E | 10.10 | 1.79 | 12.78 | 7.30 | 4.59 | <0.0001 |
| Drug Liking VAS | TA_AUE | C - E | 5.96 | 2.39 | 5.97 | 3.69 | 1.32 | <0.0001 |
| Drug Liking VAS | TA_AUE | D - E | 10.40 | 1.84 | 11.07 | 6.22 | 4.40 | <0.0001 |
| High VAS | Emax | D - B | 2.94 | 3.14 | 6 | 0 | -2 | 0.3160 |
| High VAS | Emax | C - A | 6.76 | 4.69 | 12 | 0 | -5 | 0.2043 |
| High VAS | Emax | A - E | 50.52 | 6.65 | 83 | 54 | 23 | <0.0001 |
| High VAS | Emax | B - E | 75.82 | 4.45 | 94 | 85 | 67 | <0.0001 |
| High VAS | Emax | C - E | 57.27 | 5.40 | 84 | 63 | 28 | <0.0001 |
| High VAS | Emax | D - E | 78.76 | 4.72 | 100 | 91 | 70 | <0.0001 |
| High VAS | TA_AUE | D - B | 0.41 | 1.86 | 6.38 | 1.12 | -2.68 | 0.4633 |
| High VAS | TA_AUE | C - A | 0.67 | 1.08 | 1.42 | -0.19 | -1.84 | 0.9563 |
| High VAS | TA_AUE | A - E | 9.29 | 2.32 | 11.08 | 5.55 | 1.66 | <0.0001 |
| High VAS | TA_AUE | B - E | 18.55 | 2.22 | 26.14 | 14.96 | 9.78 | <0.0001 |
| High VAS | TA_AUE | C - E | 9.97 | 2.13 | 14.63 | 5.53 | 1.76 | <0.0001 |
| High VAS | TA_AUE | D - E | 18.73 | 2.18 | 26.86 | 16.71 | 8.46 | <0.0001 |
| Take Drug Again | Emax | D - B | -2.21 | 3.47 | 2 | 0 | -7 | 0.6860 |
| Take Drug Again | Emax | C - A | 9.48 | 5.00 | 9 | 0 | -4 | 0.2492 |
| Take Drug Again | Emax | A - E | 59.39 | 7.75 | 100 | 71 | 19 | <0.0001 |
| Take Drug Again | Emax | B - E | 76.39 | 5.61 | 100 | 90 | 64 | <0.0001 |
| Take Drug Again | Emax | C - E | 68.88 | 6.44 | 100 | 85 | 43 | <0.0001 |
| Take Drug Again | Emax | D - E | 74.18 | 6.08 | 100 | 86 | 70 | <0.0001 |
| Overall Drug Liking | Emax | D - B | -2.67 | 3.33 | 2 | 0 | -10 | 0.5346 |
| Overall Drug Liking | Emax | C - A | 3.30 | 3.15 | 13 | 0 | -4 | 0.2436 |
| Overall Drug Liking | Emax | A - E | 25.33 | 3.57 | 49 | 23 | 4 | <0.0001 |
| Overall Drug Liking | Emax | B - E | 35.12 | 3.09 | 50 | 44 | 25 | <0.0001 |
| Overall Drug Liking | Emax | C - E | 28.64 | 4.11 | 50 | 32 | 19 | <0.0001 |
| Overall Drug Liking | Emax | D - E | 32.45 | 3.71 | 50 | 35 | 26 | <0.0001 |

A=Marinol 10 mg; B=Marinol 30 mg; C=Dronabinol Oral Solution 10 mg; D=Dronabinol Oral Solution 30 mg; E=placebo.
TA_AUE = time-adjusted AUE (area under the effect curve from first to last timepoint using linear trapezoidal rule divided by time between first and last timepoints)

# 1 INTRODUCTION

## 1.1 Overview

### *1.1.1 Background Information*

On 10/18/2015, CSS sent a consults review request for statistical review for the resubmitted data of 505(b) 2 NDA 205525 dronabinol oral solution (referenced IND 75228) by Insys Therapeutics (the sponsor) on 6/1/2015. The original submission of this NDA was on 8/12/2014. On October 10, 2014, FDA sent a "Refuse to file" letter to the sponsor based on the finding of "Failure to address requirements under PREA because you have provided an incomplete or inadequate pediatric study plan to support the safety and effectiveness of your product for treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who failed to respond adequately to conventional antiemetic treatments."

Dronabinol, currently a Schedule I substance, is the (-) isomer of $\Delta^9$-tetrahydrocannabinol (THC) and was approved on 5/31/1985 (Reference Listed Drug NDA 018651) marketed as Marinol (a Schedule III drug product) soft gelatin capsules formulated in sesame oil in 2.5 mg, 5 mg, and 10 mg strengths for the treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy in patients. Insys Therapeutics, Inc. has developed Dronabinol Oral Solution (5 mg/mL) to provide an alternate delivery system for the following indication:

1] Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
2] anorexia associated with weight loss in patients with AIDS.

The abuse potential of dronabinol has been evaluated in several animal models with positive effects. The data of a human abuse liability study (INS-13-017) were submitted in the NDA. Study INS-13-017 was entitled: "A Single-Dose, Double-Blind, Double-Dummy, Randomized, Placebo and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Dronabinol Oral Solution in Recreation Cannabinoid Users."

INS-13-017 exposed subjects to Dronabinol Oral Solution 10 mg and 30 mg, Marinol® Capsules 10 mg and 30 mg, and placebo, in crossover fashion. Exposure to Dronabinol Oral Solution was 35 subjects for the lower 10 mg dose, and 37 subjects for the higher 30 mg dose (Table 85). A total of 33 subjects (76.7%) completed all scheduled dosings (Table 84). Three subjects withdrew due to adverse events.

### *1.1.2 Specific Studies Reviewed*

The study INS-13-017 is reviewed. The design properties are summarized in Table 1.1. Throughout this review, Dronabinol is referred to Dronabinol oral solution, Marinol to Marinol gelatin capsule, and Placebo to  Lactose placebo tablets.

**Table 1.1 List of Studies Included in this Review**

| Study ID (Period) | Location | Design | Primary Endpoints | Treatments | Number of Subjects |
|---|---|---|---|---|---|
| INS-13-017 (11/14/2013 – 5/13/2014) | 1 site in INC Research Toronto, Inc, Canada | R, DB, DD, AC, PC, TD, five-arms crossover to evaluate the abuse potential of single dose crushed and intact IDT-001 | VAS Emax for Drug Liking | Marinol 10 mg<br>Marinol 30 mg<br>Dronabinol 10 mg<br>Dronabinol 30 mg<br>Placebo | 43 randomized and 33 subjects completed all treatment periods |

Abbreviations: DB = double-blind; DB = double-dummy; PC = placebo-controlled; AC = active-controlled; R = randomized; TD=two doses;

### 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:** | NDA205525 |
| **Company** | Insys Therapeutics, Inc. |
| **Drug** | Dronabinol oral solution |
| **CDER EDR link** | \\Cdsesub1\evsprod\NDA205525\0012 |
| **Letter date** | November 11, 2015 |

# 2 STATISTICAL EVALUATION

### 2.1 Data and Analysis Quality

The originally submitted data were not acceptable. We sent an Information Request to the sponsor on 10/30/2015 and received data resubmission on 11/11/2015 (NDA205525\0012). In general, the data in its current format 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*

To evaluate the abuse potential of Dronabinol Oral Solution compared to Marinol® (dronabinol capsule) and placebo in recreational cannabinoid users

*Secondary Objective*

- To assess the safety and tolerability of single oral doses of Dronabinol Oral Solution

#### 2.2.1.2 Study Design

This was a single-dose, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-way crossover study.

Each subject participated in a medical screening visit, a Qualification (drug discrimination) visit, 5 Treatment periods, and a Follow-up visit.

Within approximately 45 days of a standard medical screening, subjects attended a randomized, double-blind Qualification visit in which they received 20 mg Marinol® and matching placebo in a randomized crossover manner to ensure that they could discriminate the positive effects of the comparator. A washout day (Day 2) was imposed between dosing days such that each dose was separated by at least 48 hours.

- Treatment X: 20 mg Marinol® (2x 10 mg encapsulated capsules)
- Treatment Y: Placebo encapsulated tablets (2)

Subjects were required to pass the following qualification criteria to be eligible to enter the

Treatment phase:

1. Peak score (Emax) in response to 20 mg Marinol® ≥60 on Drug Liking VAS and greater than that of placebo (difference of at least 15 points).
2. Acceptable placebo response on Drug Liking VAS (ie, score between 40 to 60, inclusive).
3. Acceptable placebo and 20 mg Marinol® responses based on all other measures, as judged by the investigator or designee.
4. Safety data at 20 mg Marinol® suggested that the subject may have been able to tolerate the doses planned for the Treatment phase, as judged by the investigator or designee.
5. General behaviour suggested that the subject could successfully complete the study, as judged by the research site staff.

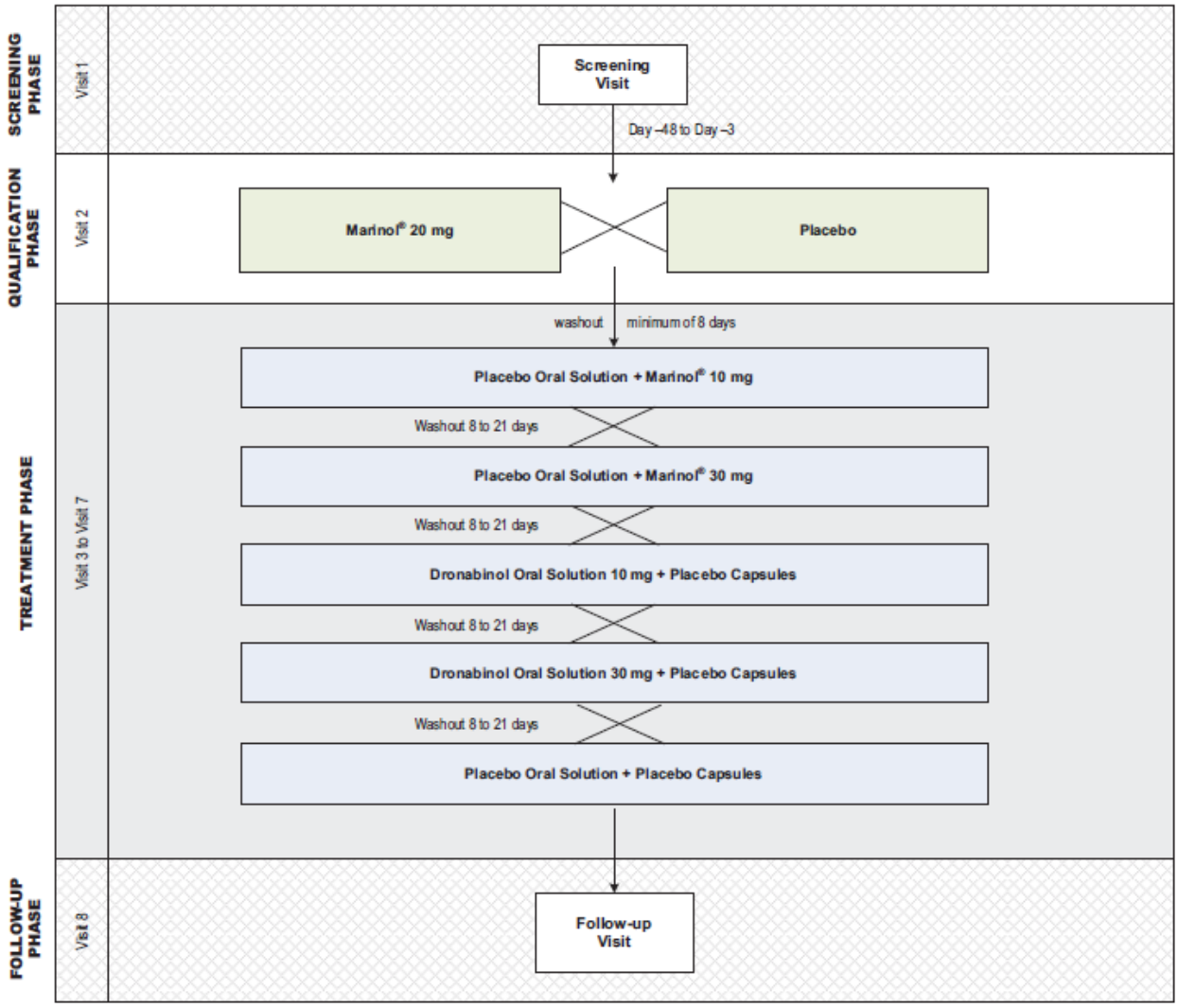
The last drug administration in the Qualification phase and the first drug administration in the Treatment phase were separated by a washout interval of at least 8 days. During the 5 treatment periods, subjects received single oral doses of each of the following treatments in a randomized, double-blind, crossover manner (two 5 x 5Williams squares):

- Treatment A: Placebo oral solution + 10 mg Marinol®
- Treatment B: Placebo oral solution + 30 mg Marinol®
- Treatment C: 10 mg Dronabinol Oral Solution + Marinol® placebo
- Treatment D: 30 mg Dronabinol Oral Solution + Marinol® placebo
- Treatment E: Placebo oral solution + Marinol® placebo

Subjects returned for an end-of-study safety Follow-up visit 5 to 10 days following the last drug administration in the Treatment phase.

The sponsor's design diagram is shown in Figure 2.1.

**Figure 2.1 Study Schematic**




2.2.1.3 Abuse Potential Measures

*Primary PD endpoint*:

The primary PD endpoint to be determined in this study was Emax on Drug Liking VAS.

Secondary PD endpoints:

- Balanced effects:
  - Drug Liking VAS (minimum score [Emin] and time-averaged area under the effect curve [TA_AUE]
  - Overall Drug Liking VAS (Emax and Emin)
  - Take Drug Again VAS (Emax)
  - SDV (Emax)

- Positive effects:
  - High VAS (Emax and TA_AUE)
  - Good Effects VAS (Emax and TA_AUE)
  - Stoned VAS (Emax and TA_AUE)
- Negative effects:
  - Bad Effects VAS (Emax and TA_AUE)
- Sedative effects:
  - Alertness/Drowsiness VAS (Emax and TA_AUE)
- Other effects:
  - Any Effects VAS (Emax and TA_AUE)
  - Other summary parameters included the time to maximum effect [TEmax] and/or time to minimum effect [TEmin]. These summary parameters were calculated, as appropriate, for all measures except for Overall Drug Liking VAS, Take Drug Again VAS, and SDV.

Data collections were planned as seen in Appendix 1 Table 1.

2.2.1.4 Analysis Population and Sample Size

*Analysis populations*

- *Randomized population*: All subjects who were assigned a randomization number in the Treatment phase
- *Safety population*: All randomized subjects who received any study treatment in the Treatment phase
- *PD Population*: All randomized subjects who completed all treatment sessions and had no major protocol deviations that would have excluded them from analysis

*Sample size estimate*

Using an estimate of the difference, which might have been expected with the 10 mg dose, a sample size of 30 completed subjects was expected to have 80% power to detect a 15-point difference in Drug Liking VAS Emax between dronabinol and placebo, using the estimated pooled SD of 19.8. Assuming a 20% dropout rate, 40 healthy male and female subjects with a history of recreational cannabinoid use were to be randomized into the Treatment phase, with the intention to complete approximately 30 subjects (at least 1 per sequence).

2.2.1.5 Statistical Methodologies used in the Sponsor's Analyses

*Hypothesis testing:*

Not specified.

*Statistical methodologies*

All PD analyses were performed using the PD population.

For PD endpoints (Emax, Emin, TA_AUE) in the Treatment phase, treatment comparisons were made between each Marinol® dose and placebo, each Dronabinol Oral Solution dose and each Marinol® dose, and each Dronabinol Oral Solution dose and placebo. The treatment comparison

analysis was performed using a mixed effects model for a crossover study. The model included treatment, period, sequence and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. If the carryover effect was found to be non-significant at the 25% level, then the term was to be dropped from the analysis model.

The residuals from the mixed effects model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed as having a normal distribution if the probability value was greater than or equal to 0.05. Parameters that did not meet this criterion were analyzed non-parametrically. Overall treatment effect was assessed using Friedman's test; pairwise treatment comparisons were assessed using the Wilcoxon signed-rank test on the within-subject differences.

The treatment comparisons to assess the abuse potential for Dronabinol Oral Solution included:

- Each dose of Marinol® (10 mg, 30 mg) compared to placebo – to validate the study sensitivity
- Each dose of Dronabinol Oral Solution (10 mg, 30 mg) compared to each dose of Marinol® (10 mg, 30 mg)
- Each dose of Dronabinol Oral Solution (10 mg, 30 mg) compared to placebo

For study validity purposes, the primary endpoint, Emax VAS for Drug Liking, was compared between the positive control (Marinol®) and placebo. If statistically significant, it would confirm the sensitivity of the study.

*Handling of Dropouts or Missing Data*

For PD analyses, missing data for subjects who were administered all scheduled study treatments for all the treatment periods were considered as random non-informative missing for analysis purposes. No imputation of missing values was performed.

*Multiple Comparisons/Multiplicity*
No Type I error adjustment was performed.

#### 2.2.1.6 Changes in the Conduct of the Study

Two amendments were made to the original study protocol (version 4.0, 28-Aug-2013).

Amendment 1 (version 5.0, 11-Nov-2013) was completed and approved prior to study initiation.

Amendment 2 (version 6.0, 16-Jan-2014) was completed and approved during the Qualification phase of the study. Twenty subjects participated in the Qualification phase under protocol version 5.0 and 73 subjects participated in Qualification phase under protocol version 6.0.

The changes from version 5.0 to version 6.0 included:

_ Removal of Addiction Research Center Inventory (ARCI) assessments and endpoints

_ Changing the doses of Dronabinol Oral Solution in the Treatment phase from 8.5 mg and

25.5 mg (bioequivalent doses to 10 mg and 30 mg Marinol®, respectively) to doses of 10 mg and 30 mg (equal milligram doses to 10 mg and 30 mg Marinol®, respectively).

These changes were recommended by the Controlled Substances Staff of the FDA. For the subjects who completed the Qualification phase of the study under protocol version 5.0, ARCI data were collected, but not listed or analyzed.

*Changes in the Planned Analyses* The following changes to the analyses planned in the study protocol were outlined in SAP version 1.0 (01-Apr-2014):

_ Emin for Alertness/Drowsiness VAS was added as a secondary PD endpoint.

_ The protocol stated that laboratory data and ECG results were to be summarized by treatment.

However, since laboratory and ECG data were not collected post-dose, these data were summarized only for all subjects combined.

_ The protocol stated that the relationship between the exposure to dronabinol (Cmax, Tmax, and

AUC) following administration of Dronabinol Oral Solution and Marinol® and subjective measures was to be explored if appropriate. However, pharmacokinetic samples were not collected for this study; therefore, this analysis was not done.

#### 2.2.1.7 Sponsor's Summary and Conclusions

Sponsor's main results are summarized in Table 2.1. Others are attached in Appendix 1.

Sponsor's conclusion:

- Statistically significant differences were observed between Marinol® and placebo on the Drug Liking VAS Emax primary endpoint, as well as secondary endpoints assessing balance, positive, sedative and other effects. Therefore, the study can be considered valid.
- No statistically significant differences were observed between comparable doses of Marinol® and Dronabinol Oral Solution (10 mg vs 10 mg or 30 mg vs 30 mg) on the Drug Liking VAS Emax primary endpoint or any of the secondary endpoints assessing balance, positive, sedative and other effects. Notably, no statistically significant differences were observed in end-of-day/ next-day measures of overall drug liking or willingness to take the drug again, and median differences were in most cases 0 or <1–2 points on 100-point VAS.
- Consistent with effects that were comparable to Marinol®, statistically significant differences were observed between Dronabinol Oral Solution and placebo on all endpoints.

Overall, the PD results from this valid study demonstrated that Dronabinol Oral Solution shows no statistically significant or clinically-relevant differences in subjective abuse potential compared to Marinol® in recreational cannabinoid users.

**Table 2.1 Comparisons of PD Parameters for the Primary (Drug Liking) and Key Secondary Endpoints (PD Population, N = 33)**

| | | | Marinol® | | Dronabinol Oral Solution | |
|---|---|---|---|---|---|---|
| Endpoint/Statistic | | Placebo (N=33) | 10 mg (N=33) | 30 mg (N=33) | 10 mg (N=33) | 30 mg (N=33) |
| $E_{max}$ | Mean (SD) | 54.2 (10.12) | 78.1 (19.08) | 89.0 (13.30) | 81.4 (16.18) | 91.7 (11.51) |
| | Median | 51.0 | 75.0 | 96.0 | 83.0 | 100.0 |
| **Overall Drug Liking VAS** | | | | | | |
| $E_{max}$ | Mean (SD) | 52.4 (9.64) | 77.7 (19.82) | 87.5 (15.55) | 81.0 (21.31) | 84.8 (17.09) |
| | Median | 50.0 | 80.0 | 95.0 | 86.0 | 86.0 |
| **Take Drug Again VAS** | | | | | | |
| $E_{max}$ | Mean (SD) | 10.4 (25.19) | 69.8 (37.70) | 86.8 (18.39) | 79.3 (32.01) | 84.6 (19.02) |
| | Median | 0.0 | 89.0 | 97.0 | 93.0 | 88.0 |
| **High VAS** | | | | | | |
| $E_{max}$ | Mean (SD) | 10.0 (21.98) | 60.5 (33.01) | 85.8 (17.90) | 67.3 (28.10) | 88.8 (15.28) |
| | Median | 0.0 | 65.0 | 90.0 | 74.0 | 97.0 |

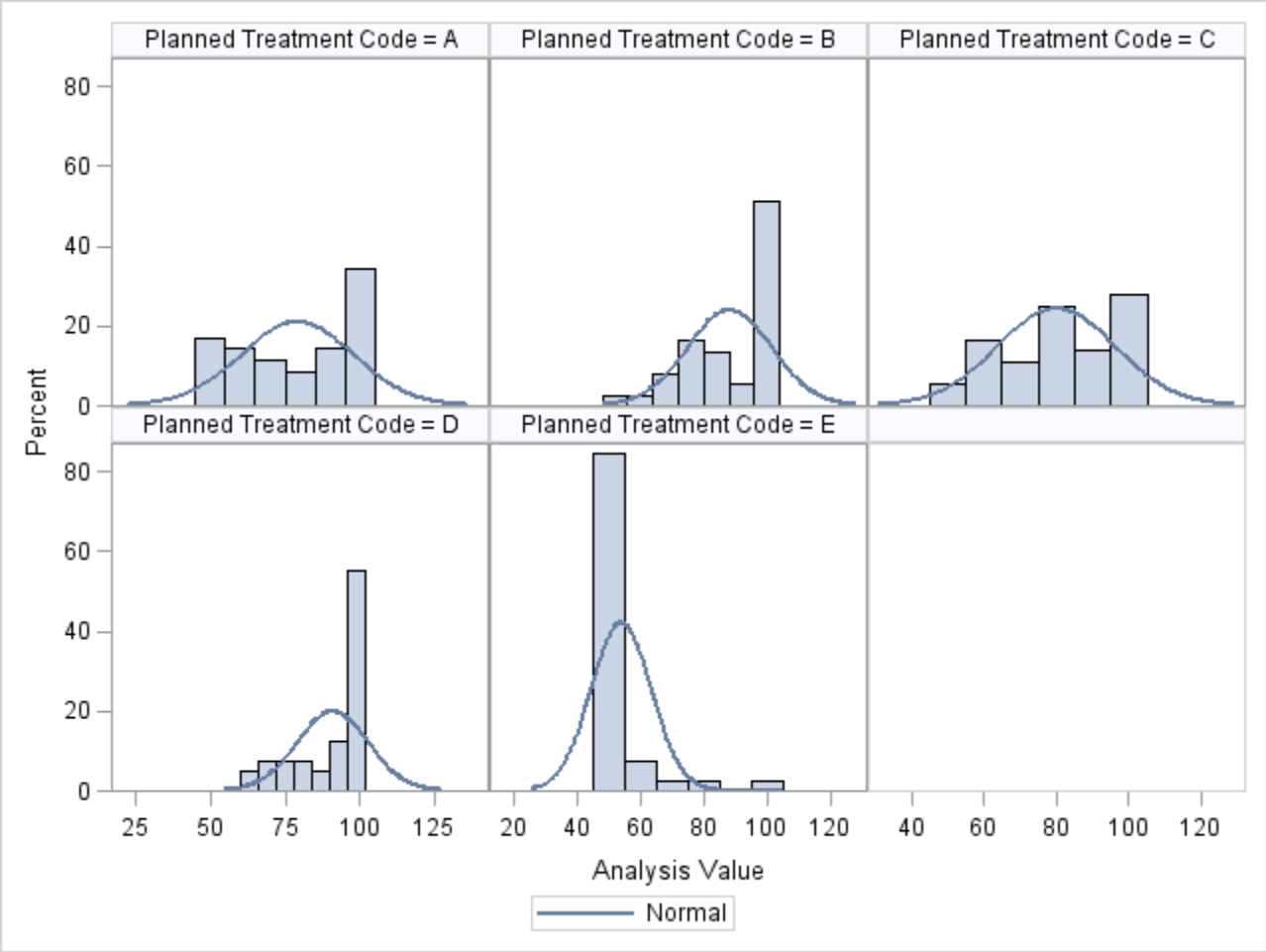
Source: sponsor's studyReport-ins-13-017.pdf Tables 8, 10, 12
Emax=maximum effect; SD=standard deviation;

## 2.2.2 Reviewer's Assessment

### 2.2.2.1 Descriptive Analysis

This reviewer checked the normality assumption of the analysis model as seen in Figure 2.1. Since the normality does not hold, non-parametric test should be used.

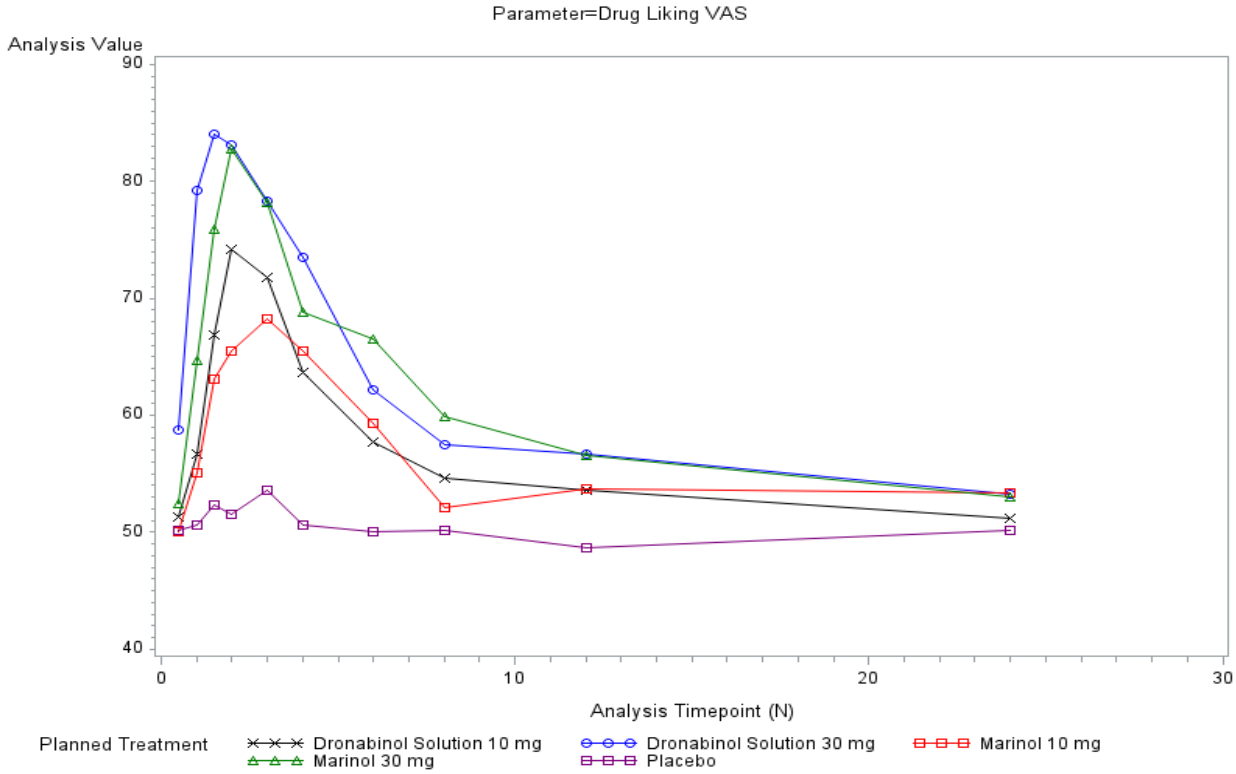
**Figure 2.2 Distribution of Drug-liking VAS $E_{max}$ by Treatment**




This reviewer verified the sponsor's descriptive primary and key secondary results shown in Table 2.1.

Figure 2.2 and 2.3 are the mean time course plots for Drug Liking VAS and High VAS, respectively. Both plots showed that the Emax of Dronabinol Oral Solution at each dose was numerically higher than that of the positive control Marinol at corresponding dose. Also, the TEmax of Dronabinol Oral Solution at each dose appeared smaller than or similar that of the positive control Marinol at corresponding dose.

## Figure 2.2 Mean Drug Liking VAS Scores Over Time (Completers, N = 33)




## Figure 2.3 Mean High VAS Scores Over Time (Completers, N =33)

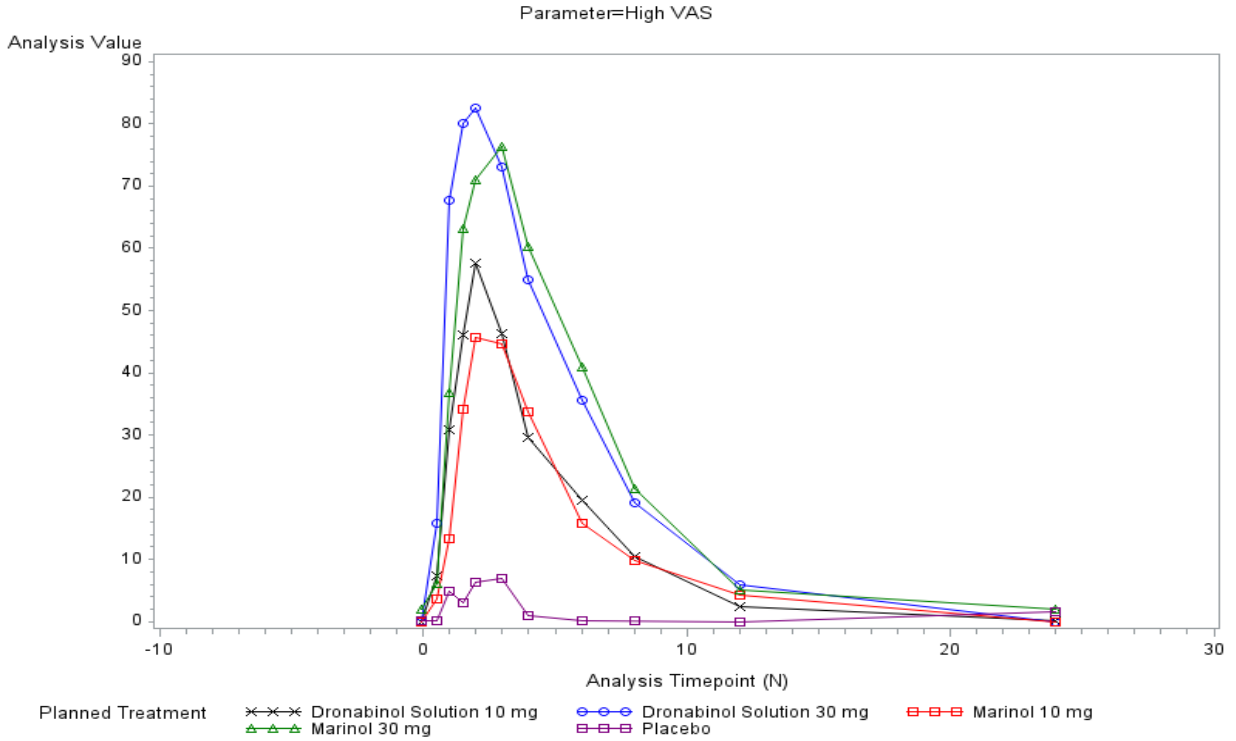
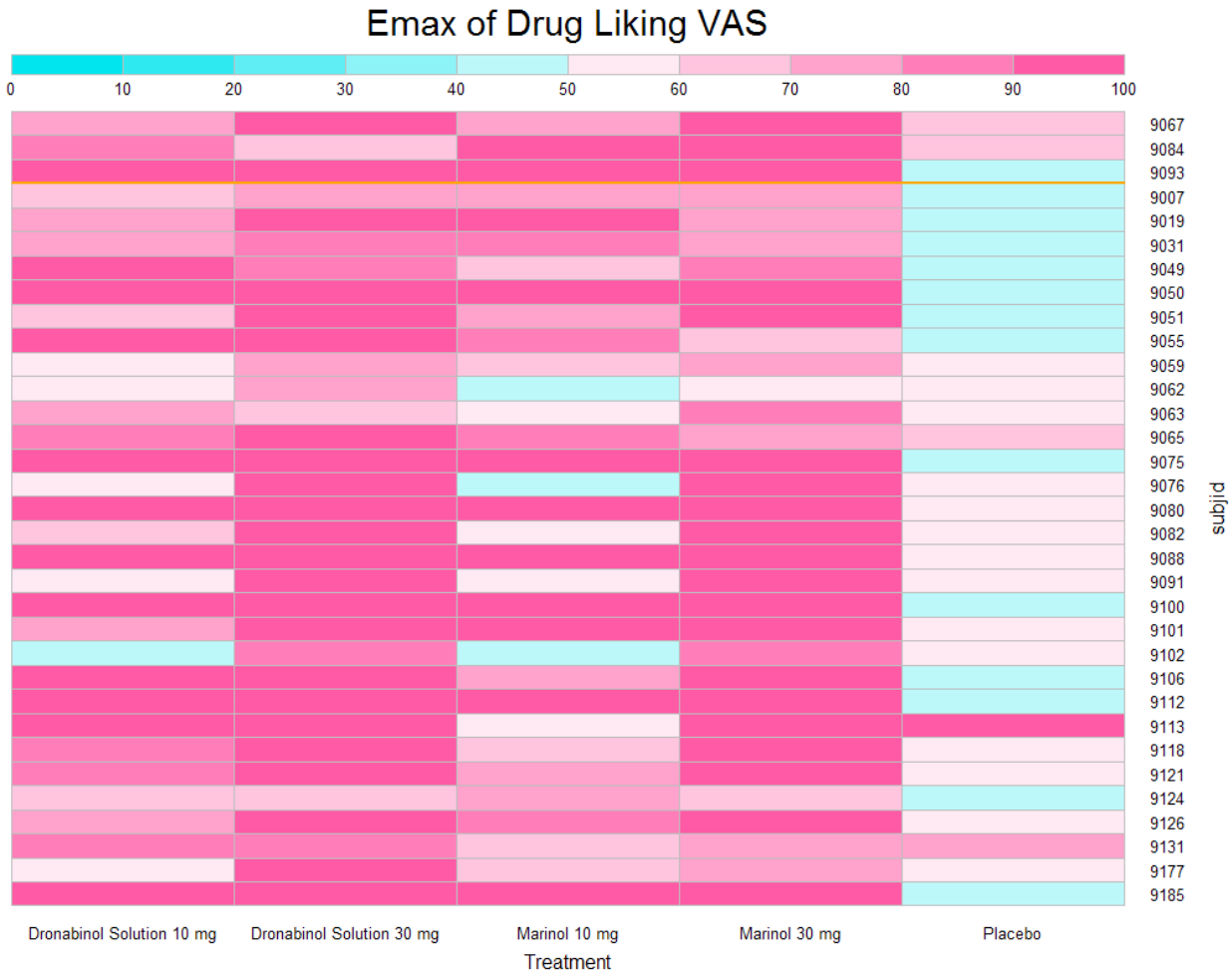


Figure 2.4 is a heat map display, which shows individual Emax responses to each treatment as measured by Drug Liking VAS. In the figure, drug disliking is shown in blue, neutral response is shown in white and drug liking is shown in pink. The subjects (n = 33) represented above the thin orange line are females (n = 3), and the subjects below the orange line are males (n = 30).

**Figure 2.4 Heat Map for the Peak Effect (Emax) of Drug Liking VAS by Treatment.**



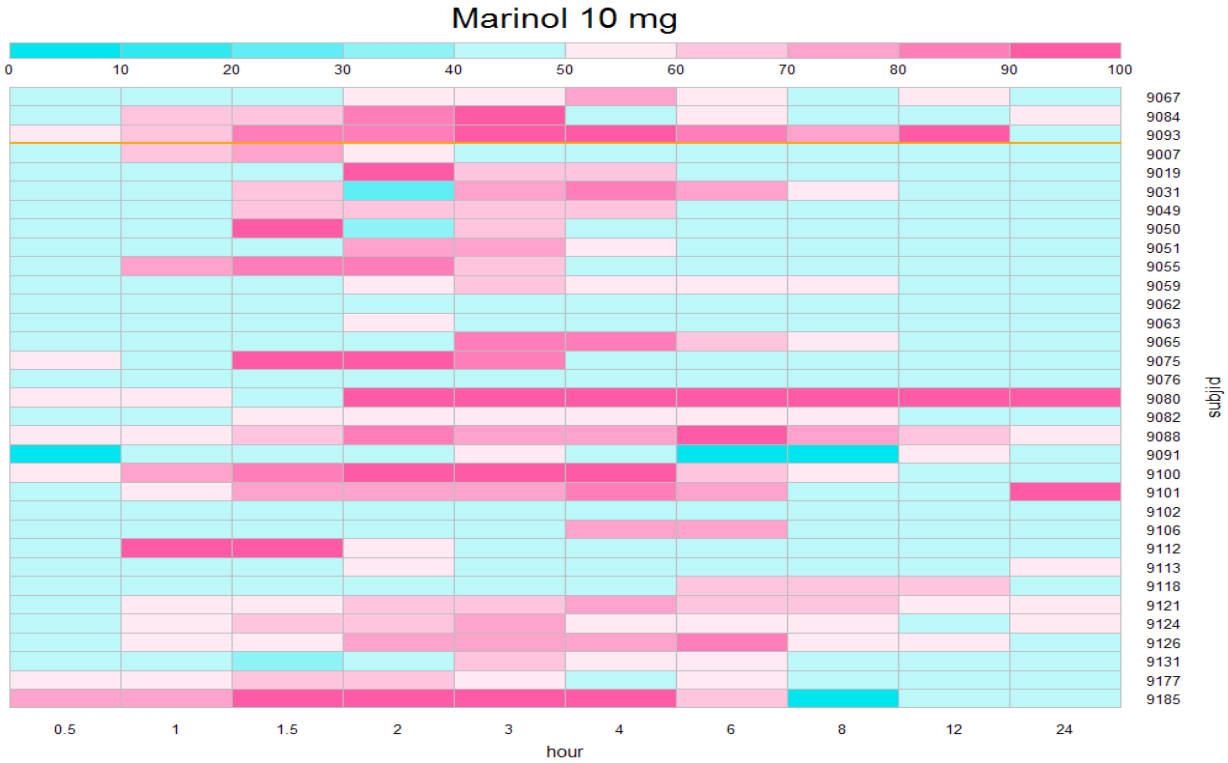

Figures 2.5A-D are the individual time course response profiles for the positive control Marinol (10 mg and 30 mg) and Dronabinol Oral Solution (10 mg and 30 mg), respectively.

One may see from the graphics the responses from all subjects at each time point, and the peak response and the duration of the peak response for each subject to the positive control and the test drug.

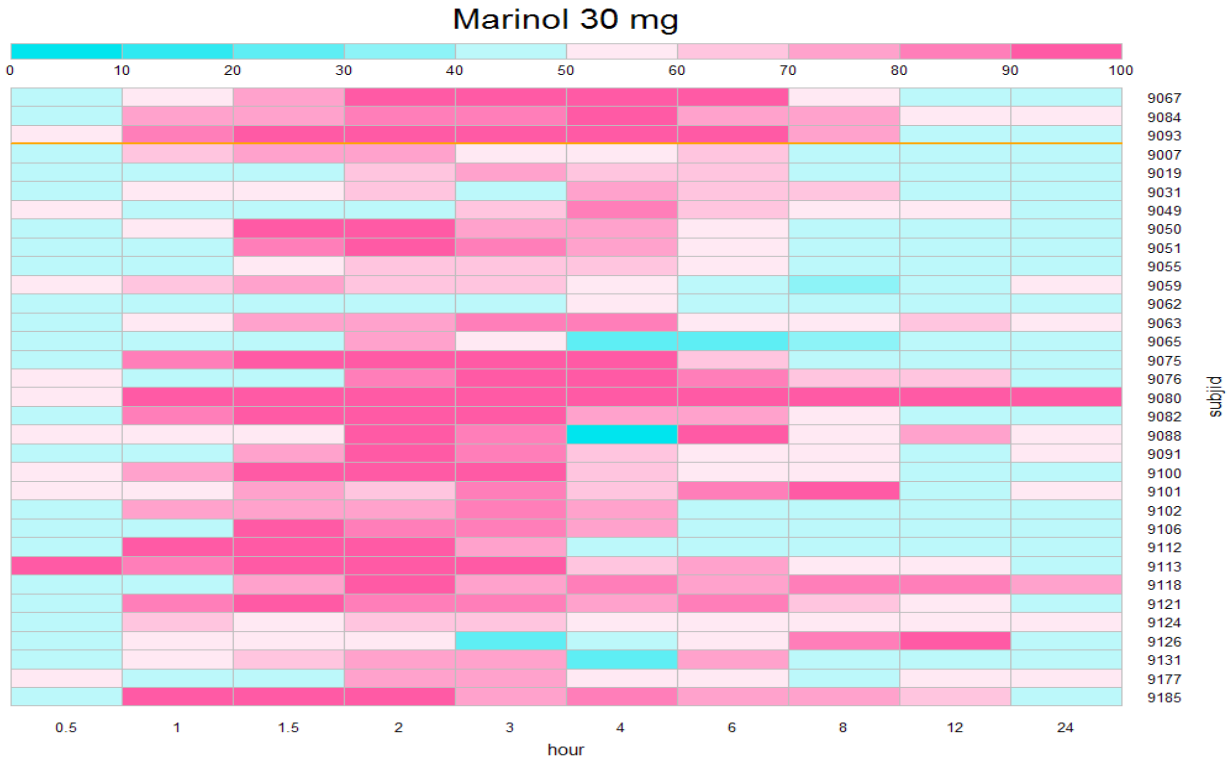
From Figures 2.4 and 2.5, one can locate the subjects who did not respond to the positive control.

**Figure 2.5 Individual time course response profiles for Drug Liking VAS.**

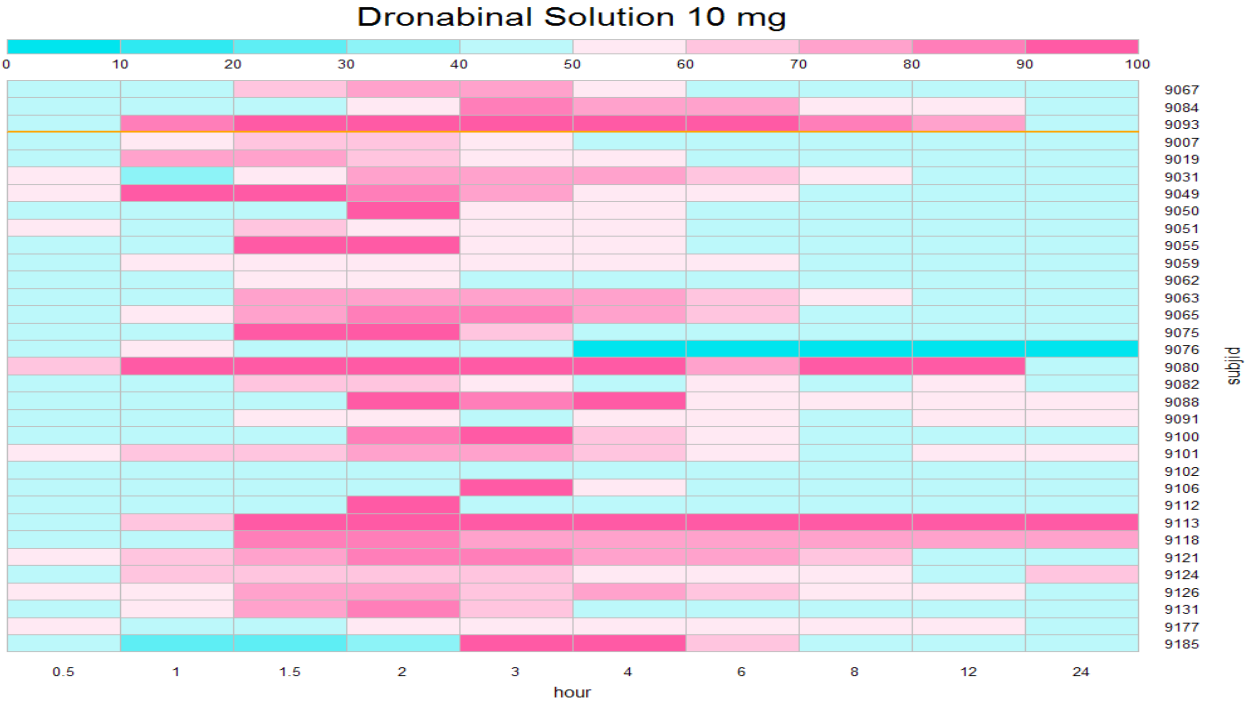
**A. Marinol 10 mg**



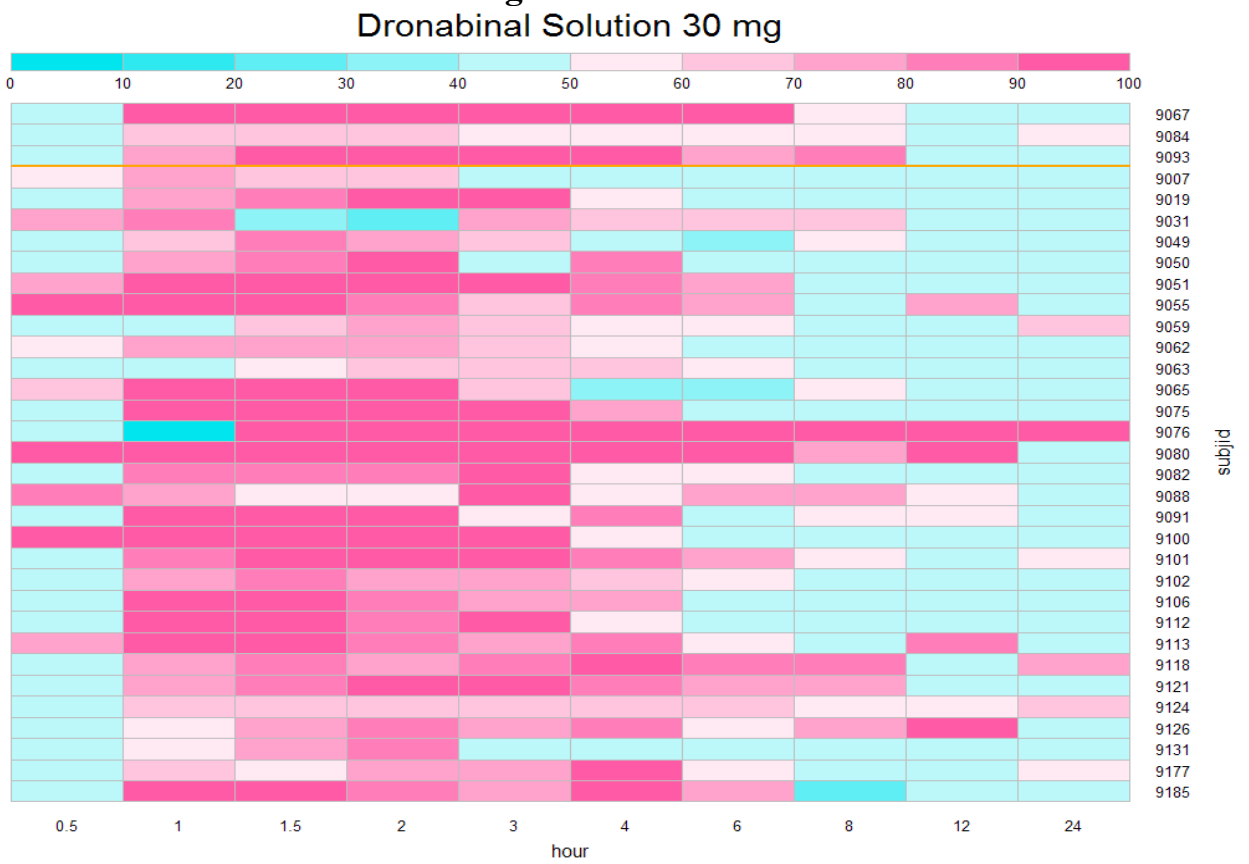

**B. Marinol 30 mg**



## C. Dronabinal Solution 10 mg




## D. Dronabinal Solution 30 mg



#### 2.2.2.2 Statistical Testing

This reviewer verified the sponsor's statistical tests on the primary and key secondary endpoints using pairwise treatment comparisons by the Wilcoxon signed-rank test on the within-subject differences as shown in Table 2.2.

These results show that

1. The differences between Marinol at each dose (A=10 mg, B=30 mg) and placebo (E) are statistically significant in the primary and key secondary PD endpoints ($p<0.0001$).
2. The differences between Dronabinol Oral Solution at each dose (C=10 mg, D=30 mg) and placebo (E) are statistically significant in the primary and key secondary PD endpoints.
3. The differences between Marinol and Dronabinol Oral Solution at either high (30 mg) or low dose (10 mg) are not statistically significant in the primary and key secondary PD endpoints.
4. The values of Dronabinol Oral Solution 30 mg are numerically larger than that of Marinol 30 mg. Similar observations are also seen at the dose of 10 mg except for the endpoints Take Drug Again and Overall Drug Liking.

More descriptive results of the PD measures for drug abuse by this reviewer are provided in Appendix 2.

## Table 2.2 Test Results for the Primary and Key Secondary Endpoints (n=33)

| PARAM | endpoint | diff | mean | STDERR | Q3 | Median | Q1 | pSignRank |
|---|---|---|---|---|---|---|---|---|
| Drug Liking VAS | Emax | D - B | 2.67 | 2.09 | 4 | 0 | 0 | 0.1071 |
| Drug Liking VAS | Emax | C - A | 3.24 | 2.53 | 10 | 0 | -3 | 0.3398 |
| Drug Liking VAS | Emax | A - E | 23.88 | 4.14 | 49 | 24 | 8 | <0.0001 |
| Drug Liking VAS | Emax | B - E | 34.79 | 2.77 | 49 | 38 | 25 | <0.0001 |
| Drug Liking VAS | Emax | C - E | 27.12 | 3.05 | 45 | 27 | 11 | <0.0001 |
| Drug Liking VAS | Emax | D - E | 37.45 | 2.69 | 50 | 43 | 32 | <0.0001 |
| Drug Liking VAS | TA_AUE | D - B | 0.30 | 1.44 | 2.60 | -0.03 | -2.49 | 0.9235 |
| Drug Liking VAS | TA_AUE | C - A | 0.03 | 2.24 | 1.36 | -0.21 | -1.13 | 0.7841 |
| Drug Liking VAS | TA_AUE | A - E | 5.92 | 1.80 | 5.86 | 3.05 | 0.93 | <0.0001 |
| Drug Liking VAS | TA_AUE | B - E | 10.10 | 1.79 | 12.78 | 7.30 | 4.59 | <0.0001 |
| Drug Liking VAS | TA_AUE | C - E | 5.96 | 2.39 | 5.97 | 3.69 | 1.32 | <0.0001 |
| Drug Liking VAS | TA_AUE | D - E | 10.40 | 1.84 | 11.07 | 6.22 | 4.40 | <0.0001 |
| High VAS | Emax | D - B | 2.94 | 3.14 | 6 | 0 | -2 | 0.3160 |
| High VAS | Emax | C - A | 6.76 | 4.69 | 12 | 0 | -5 | 0.2043 |
| High VAS | Emax | A - E | 50.52 | 6.65 | 83 | 54 | 23 | <0.0001 |
| High VAS | Emax | B - E | 75.82 | 4.45 | 94 | 85 | 67 | <0.0001 |
| High VAS | Emax | C - E | 57.27 | 5.40 | 84 | 63 | 28 | <0.0001 |
| High VAS | Emax | D - E | 78.76 | 4.72 | 100 | 91 | 70 | <0.0001 |
| High VAS | TA_AUE | D - B | 0.41 | 1.86 | 6.38 | 1.12 | -2.68 | 0.4633 |
| High VAS | TA_AUE | C - A | 0.67 | 1.08 | 1.42 | -0.19 | -1.84 | 0.9563 |
| High VAS | TA_AUE | A - E | 9.29 | 2.32 | 11.08 | 5.55 | 1.66 | <0.0001 |
| High VAS | TA_AUE | B - E | 18.55 | 2.22 | 26.14 | 14.96 | 9.78 | <0.0001 |
| High VAS | TA_AUE | C - E | 9.97 | 2.13 | 14.63 | 5.53 | 1.76 | <0.0001 |
| High VAS | TA_AUE | D - E | 18.73 | 2.18 | 26.86 | 16.71 | 8.46 | <0.0001 |
| Take Drug Again | Emax | D - B | -2.21 | 3.47 | 2 | 0 | -7 | 0.6860 |
| Take Drug Again | Emax | C - A | 9.48 | 5.00 | 9 | 0 | -4 | 0.2492 |
| Take Drug Again | Emax | A - E | 59.39 | 7.75 | 100 | 71 | 19 | <0.0001 |
| Take Drug Again | Emax | B - E | 76.39 | 5.61 | 100 | 90 | 64 | <0.0001 |
| Take Drug Again | Emax | C - E | 68.88 | 6.44 | 100 | 85 | 43 | <0.0001 |
| Take Drug Again | Emax | D - E | 74.18 | 6.08 | 100 | 86 | 70 | <0.0001 |
| Overall Drug Liking | Emax | D - B | -2.67 | 3.33 | 2 | 0 | -10 | 0.5346 |
| Overall Drug Liking | Emax | C - A | 3.30 | 3.15 | 13 | 0 | -4 | 0.2436 |
| Overall Drug Liking | Emax | A - E | 25.33 | 3.57 | 49 | 23 | 4 | <0.0001 |
| Overall Drug Liking | Emax | B - E | 35.12 | 3.09 | 50 | 44 | 25 | <0.0001 |
| Overall Drug Liking | Emax | C - E | 28.64 | 4.11 | 50 | 32 | 19 | <0.0001 |
| Overall Drug Liking | Emax | D - E | 32.45 | 3.71 | 50 | 35 | 26 | <0.0001 |

A=Marinol 10 mg; B=Marinol 30 mg; C=Dronabinol Oral Solution 10 mg; D=Dronabinol Oral Solution 30 mg; E=placebo.
TA_AUE = time-adjusted AUE (area under the effect curve from first to last timepoint using linear trapezoidal rule divided by time between first and last timepoints).

### 2.2.2.3 Conclusion

#### *2.2.2.3.1 Statistical Issues*

- The null hypotheses were not defined for both the primary analysis and the analysis of secondary PD endpoints
- A total of 10 subjects (23%) discontinued from the study prior to completion in the Treatment phase. Reasons for discontinuation were categorized in the following:

    1. Three subjects withdrew (Subject 9040 after taking the placebo treatment; Subject 9157 from 10 mg Dronabinol Oral Solution; and Subject 9166 after receiving 30 mg Dronabinol Oral Solution)
    2. Three subjects had treatment-emergent adverse events (Subjects 9015 and 9139after receiving 30 mg Marinol and Subject 9081 discontinued after receiving 30 mg Dronabinol Oral Solution)
    3. Four subjects discontinued due to positive urine drug screens (Subjects 9001, 9011, and 9069 after receiving 30 mg Dronabinol Oral Solution, Subject 9155 after receiving 30 mg Marinol)

    There were a total of 5 subjects discontinued after receiving 30 mg Dronabinol Oral Solution while 3 after taking 30 mg Marinol. The sponsor did not replace these non-completers, leading to an unbalanced Williams square design in estimation of mean differences.

#### *2.2.2.3.2 Conclusions and Recommendations*

The numbers of completers were 33 (77%) with a total of 43 subjects randomized to the treatment phase. Among the 10 subjects who discontinued in the Treatment phase, 5 after receiving 30 mg Dronabinol Oral Solution while 3 after taking 30 mg Marinol.

The descriptive analysis of the primary and some key secondary endpoints (peak VAS of Overall drug liking, Take drug Again, and High) by this reviewer are the same as those by the sponsor (see Table 2.1 and Appendix 2 Table 1). This reviewer confirmed the sponsor's results about the abuse liability of Dronabinol Oral Solution (10 mg and 30 mg) using the positive control Marinol (10 mg and 30 mg), based on the pre-defined primary and secondary endpoints: peak effect of Drug Liking (at the moment) and HighVAS and areas under the VAS curves during the treatment period, 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). The differences between Marinol and Dronabinol Oral Solution at either high (30 mg) or low dose (10 mg) are not statistically significant in the primary and key secondary PD endpoints. However, the endpoint values of Dronabinol Oral Solution 30 mg are numerically larger than that of Marinol 30 mg. The similar observations are also seen at the dose of 10 mg except for the endpoints Take Drug Again and Overall Drug Liking.

### *2.2.2.3.3 Labeling Recommendations*

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

1. In the subsection 9.2 of Section 9 (b) (4), in the 6th paragraph:

   (b) (4)

   Please state explicitly the "differences" between what treatments.

2. In the subsection 9.3 of Section 9 (b) (4), on p11 the second paragraph:

   (b) (4)

# 3 APPENDIX

## 3.1 Appendix 1

**Appendix 1 Table 1 Schedule of Assessments**

| Assessment | Screening | Qualification | | | | | | | | | | | | Treatment Period 1 to Treatment Period 5 | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit: | 1 | 2 | | | | | | | | | | | | 3 to 7 | | | | | | | | | | | | | | 8 |
| Day: | -47 to -3 | -2 | -1 | 1, 3 | | | | | | | | | 2, 4 | -2 | -1 | 1 | | | | | | | | | | | | 2 | — |
| | | | | Assessment time points (hours) | | | | | | | | | | | | Assessment time points (hours) | | | | | | | | | | | | | |
| **Subject Review** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | X[a] | | | | | | | | | | | | X[a] | | | | | | | | | | | | | | |
| Medication and Recreational Drug Use History | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study Restrictions Review | | X | | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| DSM-IV | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical Examination | X | X[b] | | | | | | | | | | | | X[b] | | | | | | | | | | | | | | X |
| Height, Weight, BMI | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum Pregnancy | X | | | | | | | | | | | | | X | | | | | | | | | | | | | | X |
| Urine Pregnancy | | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| FSH (post-menopausal women) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HIV, Hepatitis B and C | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tuberculosis | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Vital Signs | X | | X | pre | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | | 24 | | X | pre | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | 12 | 24 | X |
| Oral Temperature | X | | X | pre | | | | | | | | | | | X | pre | | | | | | | | | | | X |
| 12-Lead ECG | X | | X | | | | | | | | | | | | X | | | | | | | | | | | | X |
| Urine Drug Screen | X | X | | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Breath Alcohol | X | X | | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Clinical Laboratory | X | | | | | | | | | | | | | X | | | | | | | | | | | | | X |
| Concomitant Medications | | X | X | < | - | - | - | - | - | - | - | > | | X | X | < | - | - | - | - | - | - | - | - | - | > | X |
| AE Monitoring[c] | | X | X | pre | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | | 24 | X | X | pre | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | 12 | 24 | X |
| **Pharmacodynamics** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Training/Practice | | | X | | | | | | | | | | | | X | | | | | | | | | | | | |
| Drug-Specific VAS[d] | | | | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | | 24 | | | | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | 12 | 24 | |
| Other VAS[e] | | | | pre | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | | 24 | | | pre | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | 12 | 24 | |
| ODL, TDA, SDV | | | | | | | | | | | 8 | | 24 | | | | | | | | | | | | 12 | 24 | |
| **Study Administration** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization | | | | pre[f] | | | | | | | | | | | | pre[g] | | | | | | | | | | | | |
| Admission | | X | | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Drug Administration | | | | 0 | | | | | | | | | | | | 0 | | | | | | | | | | | | |
| Discharge | | | | | | | | | | | | | X[h] | | | | | | | | | | | | | | X | |

AE=adverse event; BMI=body mass index; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders - Fourth Revision; ECG=electrocardiogram; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; ODL=Overall Drug Liking VAS; pre=pre-dose; SDV=Subjective Drug Value; TDA=Take Drug Again VAS; VAS=visual analog scale.

a Focusing on any changes since the last visit
b Symptom-directed physical examination performed at the investigator's discretion
c Spontaneous AE reporting was continuous throughout the study; however, at specified time points, AE questioning was performed using a non-leading question.
d Drug Liking VAS, Good Effects VAS, Bad Effects VAS, and Any Effects VAS
e High VAS, Stoned VAS, and Alertness/Drowsiness VAS
f Day 1 only
g Treatment Period 1 only
h Day 4 only
Source: sponsor's study report ins-13-017.pdf Table 2.

**Appendix 1 Table 2 Subject Disposition During the Treatment Phase (All Subjects)**

| Subject Disposition | Total n (%) |
|---|---|
| Randomized to Treatment phase | 43 |
| Completed all treatment visits | 33 (76.7) |
| Completed Treatment Period 1 | 43 (100) |
| Completed Treatment Period 2 | 41 (95.3) |
| Completed Treatment Period 3 | 37 (86.0) |
| Completed Treatment Period 4 | 33 (76.7) |
| Completed Treatment Period 5 | 33 (76.7) |
| Safety population | 43 (100) |
| PD population | 33 (76.7) |
| Early withdrawal from the study | 10 (23.3) |

Source: sponsor's study report ins-13-017.pdf Table 3.

**Appendix 1 Table 3 Drug Liking VAS Emax Results for the Qualification Phase (PD Population)**

| | Placebo N=33 | 20 mg Marinol® N=33 |
|---|---|---|
| Mean (SD) | 50.5 (0.94) | 95.9 (6.78) |
| Median | 50.0 | 100.0 |
| Range | 50–55 | 75–100 |

Source: sponsor's study report ins-13-017.pdf Table 7.

**Appendix 1 Table 4 Selected Descriptive Statistics of Derived Parameters for Drug Liking VAS (PD Population)**

| | | | Marinol® | | Dronabinol Oral Solution | |
|---|---|---|---|---|---|---|
| Endpoint/Statistic | | Placebo (N=33) | 10 mg (N=33) | 30 mg (N=33) | 10 mg (N=33) | 30 mg (N=33) |
| $E_{max}$ | Mean (SD) | 54.2 (10.12) | 78.1 (19.08) | 89.0 (13.30) | 81.4 (16.18) | 91.7 (11.51) |
| | Median | 51.0 | 75.0 | 96.0 | 83.0 | 100.0 |
| $TE_{max}$ (h) | Median | 0.500 | 2.983 | 2.000 | 2.000 | 1.500 |
| | Range | 0.48, 12.00 | 0.50, 24.00 | 1.00, 12.00 | 0.50, 4.00 | 0.50, 12.00 |
| $E_{min}$ | Mean (SD) | 48.3 (8.69) | 45.5 (12.61) | 45.6 (11.43) | 47.3 (9.71) | 46.5 (9.22) |
| | Median | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| $TE_{min}$ (h) | Median | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 |
| | Range | 0.48, 24.00 | 0.48, 24.00 | 0.48, 24.00 | 0.48, 24.00 | 0.48, 24.00 |
| TA_AUE | Mean (SD) | 49.90 (2.879) | 55.83 (10.064) | 60.00 (9.779) | 55.86 (13.899) | 60.30 (10.050) |
| | Median | 50.02 | 53.05 | 57.30 | 53.16 | 56.30 |

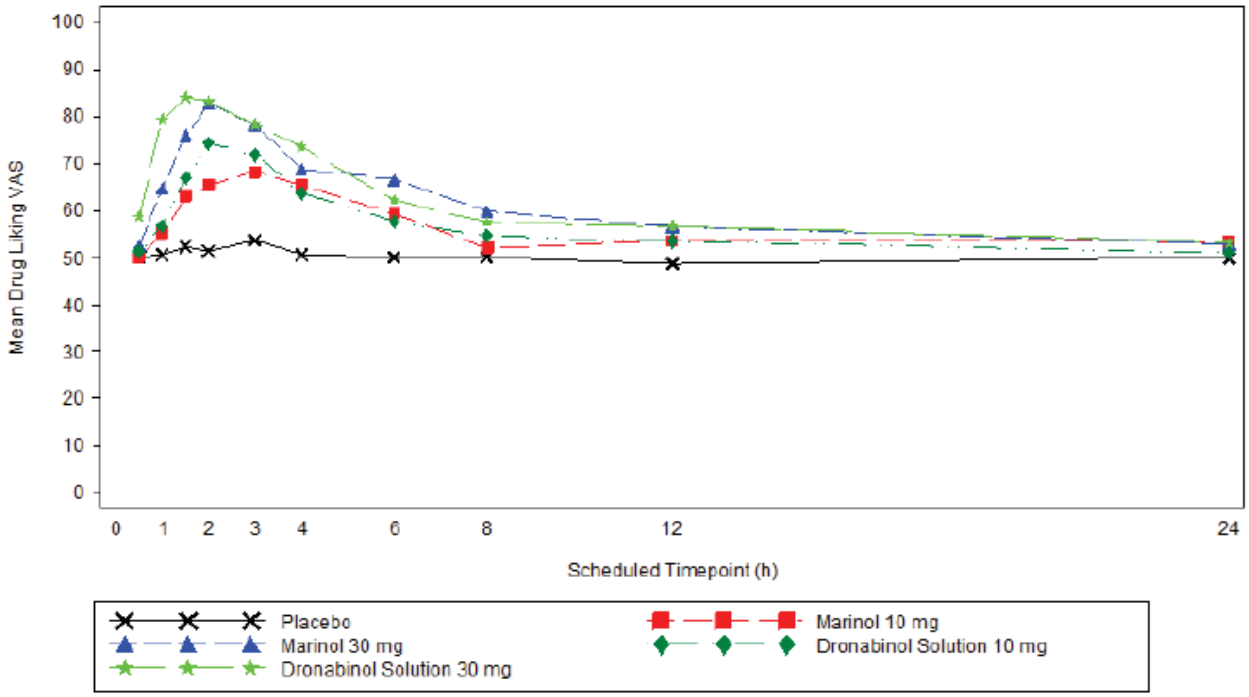
Source: sponsor's study report ins-13-017.pdf Table 8.

**Appendix 1 Table 5 Analysis Results for Drug Liking VAS Emax and TA_AUE (PD Population)**

| | $E_{max}$ (Primary Endpoint) | | TA_AUE (Secondary Endpoint) | |
|---|---|---|---|---|
| | Median Difference | *P* Value | Median Difference | *P* value |
| Overall Treatment Effect | — | <0.001 | — | <0.001 |
| **Pairwise Comparisons** | | | | |
| **Marinol vs Placebo** | | | | |
| Marinol 10 mg - Placebo | 24.0 | <0.001 | 3.05 | <0.001 |
| Marinol 30 mg - Placebo | 38.0 | <0.001 | 7.30 | <0.001 |
| **Dronabinol Oral Solution vs Marinol** | | | | |
| Dronabinol Solution 10 mg - Marinol 10 mg | 0.0 | 0.340 | -0.21 | 0.784 |
| Dronabinol Solution 30 mg - Marinol 30 mg | 0.0 | 0.107 | -0.03 | 0.923 |
| **Dronabinol Oral Solution vs Placebo** | | | | |
| Dronabinol Solution 10 mg - Placebo | 27.0 | <0.001 | 3.69 | <0.001 |
| Dronabinol Solution 30 mg - Placebo | 43.0 | <0.001 | 6.22 | <0.001 |

Source: sponsor's study report ins-13-017.pdf Table 9.

## Appendix 1 Figure 1 Mean Drug Liking VAS Scores Over Time (PD Population)




Source: sponsor's study report ins-13-017.pdf Figure 2.

**Appendix 1 Table 6 Summary of Analysis Results (P Values) for Subjective Measures (PD Set)**

| Measure/ Endpoint | Marinol® vs Placebo | | Marinol® vs Dronabinol Solution | | Dronabinol vs Placebo | |
|---|---|---|---|---|---|---|
| | 10 mg | 30 mg | 10 mg vs 10 mg | 30 mg vs 30 mg | 10 mg | 30 mg |
| **Balance of Effects** | | | | | | |
| Drug Liking VAS (primary) | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.340 (0.0) | 0.107 (0.0) | <0.001 (+) | <0.001 (+) |
| TA_AUE | <0.001 (+) | <0.001 (+) | 0.784 (–0.21) | 0.923 (-0.03) | <0.001 (+) | <0.001 (+) |
| Overall Drug Liking VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.244 (0.0) | 0.535 (0.0) | <0.001 (+) | <0.001 (+) |
| $E_{min}$ | <0.001 (+) | <0.001 (+) | 0.604 (0.0) | 0.855 (0.0) | <0.001 (+) | <0.001 (+) |
| Take Drug Again VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.249 (0.0) | 0.686 (0.0) | <0.001 (+) | <0.001 (+) |
| Subjective Drug Value (SDV) | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.504 (0.0) | 0.496 (0.0) | <0.001 (+) | <0.001 (+) |
| **Positive Effects** | | | | | | |
| Good Effects VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.256 (0.0) | 0.920 (0.0) | <0.001 (+) | <0.001 (+) |
| TA_AUE | <0.001 (+) | <0.001 (+) | 0.466 (-0.32) | 0.951 (-0.45) | <0.001 (+) | <0.001 (+) |
| High VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.204 (0.0) | 0.316 (0.0) | <0.001 (+) | <0.001 (+) |
| TA_AUE | <0.001 (+) | <0.001 (+) | 0.949 (-0.19) | 0.463 (1.12) | <0.001 (+) | <0.001 (+) |
| Stoned VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.743 (0.0) | 0.538 (0.0) | <0.001 (+) | <0.001 (+) |
| TA_AUE | <0.001 (+) | <0.001 (+) | 0.553 (–0.08) | 0.841 (0.65) | <0.001 (+) | <0.001 (+) |
| **Negative Effects** | | | | | | |
| Bad Effects VAS | | | | | | |
| $E_{max}$ | 0.012 (+) | <.001 (+) | 0.763 (0.0) | 0.424 (0.0) | 0.012 (+) | <0.001 (+) |
| TA_AUE | 0.119 | 0.003 (+) | 0.511 (0.0) | 0.378 (0.0) | 0.024 (+) | 0.003 (+) |
| **Sedative and Other Effects** | | | | | | |
| Alertness/Drowsiness VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.635 (1.4) | 0.901 (0.4) | <0.001 (+) | <0.001 (+) |
| $E_{min}$ | 0.005 (+) | <0.001 (+) | 0.927 (0.0) | 0.393 (0.0) | <0.001 (+) | <0.001 (+) |
| Any Effects VAS | | | | | | |
| $E_{max}$ | <0.001 (+) | <0.001 (+) | 0.322 (0.0) | 0.895 (0.0) | <0.001 (+) | <0.001 (+) |
| TA_AUE | <0.001 (+) | <0.001 (+) | 0.533 (-1.16) | 0.993 (-1.02) | <0.001 (+) | <0.001 (+) |

Source: sponsor's study report ins-13-017.pdf Table 18.

## 3.2 Appendix 2

**Appendix 2 Table 1 Summary of endpoint measures for drug abuse (Completers Set)**

| ENDPOINT, EP[1] | EP[2] | TRT[3] | n | mean | SE | min | Q1 | median | Q3 | max |
|---|---|---|---|---|---|---|---|---|---|---|
| Alertness/Drowsiness | Emax | C | 33 | 71.24 | 3.36 | 50 | 51 | 66 | 92 | 100 |
| Alertness/Drowsiness | Emax | D | 33 | 76.52 | 3.09 | 50 | 61 | 75 | 93 | 100 |
| Alertness/Drowsiness | Emax | A | 33 | 70.03 | 3.32 | 50 | 51 | 64 | 86 | 100 |
| Alertness/Drowsiness | Emax | B | 33 | 74.97 | 3.46 | 50 | 51 | 75 | 97 | 100 |
| Alertness/Drowsiness | Emax | E | 33 | 60.39 | 2.99 | 50 | 50 | 51 | 63 | 100 |
| Alertness/Drowsiness | Emin | C | 33 | 35.76 | 3.35 | 0 | 22 | 37 | 50 | 100 |
| Alertness/Drowsiness | Emin | D | 33 | 28.64 | 3.96 | 0 | 8 | 35 | 48 | 100 |
| Alertness/Drowsiness | Emin | A | 33 | 34.64 | 3.00 | 0 | 24 | 39 | 50 | 62 |
| Alertness/Drowsiness | Emin | B | 33 | 30.15 | 4.04 | 0 | 11 | 27 | 50 | 100 |
| Alertness/Drowsiness | Emin | E | 33 | 44.70 | 2.87 | 0 | 42 | 50 | 50 | 100 |
| Alertness/Drowsiness | TA_AUE | C | 33 | 52.55 | 2.14 | 26.92 | 48.65 | 50.74 | 52.90 | 100 |
| Alertness/Drowsiness | TA_AUE | D | 32 | 51.71 | 2.75 | 23.82 | 43.81 | 50.36 | 55.45 | 100 |
| Alertness/Drowsiness | TA_AUE | A | 33 | 51.83 | 1.81 | 32.15 | 47.75 | 50.25 | 54.38 | 92.05 |
| Alertness/Drowsiness | TA_AUE | B | 33 | 51.73 | 2.43 | 20.64 | 44.57 | 50.04 | 56.79 | 100 |
| Alertness/Drowsiness | TA_AUE | E | 33 | 54.20 | 1.94 | 45.77 | 50.00 | 50.08 | 51.16 | 100 |
| Alertness/Drowsiness | TEmax | C | 33 | 3.54 | 0.98 | 0.5 | 1 | 1.5 | 3.02 | 24 |
| Alertness/Drowsiness | TEmax | D | 33 | 3.11 | 1.01 | 0.5 | 1 | 1 | 2 | 24 |
| Alertness/Drowsiness | TEmax | A | 33 | 4.83 | 1.29 | 0.48 | 1.48 | 2 | 3 | 24 |
| Alertness/Drowsiness | TEmax | B | 33 | 5.24 | 1.33 | 0.48 | 0.98 | 1.5 | 4 | 24 |
| Alertness/Drowsiness | TEmax | E | 33 | 3.30 | 1.03 | 0.48 | 0.5 | 0.5 | 3 | 24 |
| Alertness/Drowsiness | TEmin | C | 33 | 2.68 | 0.36 | 0.48 | 0.5 | 2 | 4 | 6 |
| Alertness/Drowsiness | TEmin | D | 33 | 2.88 | 0.39 | 0.5 | 0.5 | 2.98 | 4 | 8 |
| Alertness/Drowsiness | TEmin | A | 33 | 4.16 | 0.83 | 0.48 | 0.5 | 3 | 6 | 24 |
| Alertness/Drowsiness | TEmin | B | 33 | 3.60 | 0.49 | 0.48 | 1 | 3 | 6 | 12 |
| Alertness/Drowsiness | TEmin | E | 33 | 1.72 | 0.39 | 0.48 | 0.5 | 0.5 | 1.5 | 8 |
| Any Effects VAS | Emax | C | 33 | 72.39 | 4.80 | 0 | 50 | 80 | 100 | 100 |
| Any Effects VAS | Emax | D | 33 | 90.42 | 2.29 | 59 | 78 | 100 | 100 | 100 |
| Any Effects VAS | Emax | A | 33 | 63.91 | 6.02 | 0 | 38 | 69 | 95 | 100 |
| Any Effects VAS | Emax | B | 33 | 89.88 | 3.12 | 11 | 84 | 96 | 100 | 100 |
| Any Effects VAS | Emax | E | 33 | 8.58 | 3.49 | 0 | 0 | 0 | 4 | 69 |
| Any Effects VAS | TA_AUE | C | 33 | 13.32 | 2.84 | 0.00 | 3.71 | 6.93 | 14.73 | 74.47 |
| Any Effects VAS | TA_AUE | D | 33 | 25.02 | 2.70 | 4.57 | 13.48 | 19.50 | 32.30 | 67.74 |
| Any Effects VAS | TA_AUE | A | 33 | 12.88 | 2.82 | 0.00 | 3.92 | 8.41 | 14.69 | 69.14 |
| Any Effects VAS | TA_AUE | B | 33 | 25.27 | 3.32 | 0.70 | 11.67 | 24.76 | 32.11 | 98.94 |
| Any Effects VAS | TA_AUE | E | 33 | 1.22 | 0.66 | 0.00 | 0.00 | 0.00 | 0.08 | 19.93 |
| Any Effects VAS | TEmax | C | 33 | 1.88 | 0.13 | 0.5 | 1.5 | 1.98 | 2 | 4 |
| Any Effects VAS | TEmax | D | 33 | 1.47 | 0.13 | 0.5 | 1 | 1.5 | 1.98 | 4 |
| Any Effects VAS | TEmax | A | 33 | 2.71 | 0.28 | 0.48 | 1.5 | 2 | 3.98 | 6.02 |
| Any Effects VAS | TEmax | B | 33 | 2.48 | 0.17 | 1 | 2 | 2 | 3 | 4 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Any Effects VAS | TEmax | E | 33 | 0.92 | 0.15 | 0.48 | 0.5 | 0.5 | 0.5 | 3 |
| Bad Effects VAS | Emax | C | 33 | 16.12 | 4.79 | 0 | 0 | 0 | 20 | 95 |
| Bad Effects VAS | Emax | D | 33 | 22.85 | 5.10 | 0 | 0 | 6 | 33 | 100 |
| Bad Effects VAS | Emax | A | 33 | 13.12 | 4.26 | 0 | 0 | 0 | 16 | 100 |
| Bad Effects VAS | Emax | B | 33 | 25.64 | 5.52 | 0 | 0 | 12 | 50 | 100 |
| Bad Effects VAS | Emax | E | 33 | 4.64 | 2.65 | 0 | 0 | 0 | 0 | 67 |
| Bad Effects VAS | TA_AUE | C | 33 | 1.49 | 0.61 | 0.00 | 0.00 | 0.00 | 1.17 | 17.90 |
| Bad Effects VAS | TA_AUE | D | 33 | 3.53 | 1.25 | 0.00 | 0.00 | 0.51 | 2.82 | 31.74 |
| Bad Effects VAS | TA_AUE | A | 33 | 2.74 | 1.31 | 0.00 | 0.00 | 0.00 | 0.55 | 38.32 |
| Bad Effects VAS | TA_AUE | B | 33 | 4.56 | 1.47 | 0.00 | 0.00 | 0.62 | 3.21 | 36.84 |
| Bad Effects VAS | TA_AUE | E | 33 | 2.06 | 1.59 | 0.00 | 0.00 | 0.00 | 0.00 | 50.33 |
| Bad Effects VAS | TEmax | C | 33 | 1.32 | 0.24 | 0.48 | 0.50 | 0.50 | 1.98 | 6.02 |
| Bad Effects VAS | TEmax | D | 33 | 2.66 | 0.49 | 0.48 | 0.5 | 1.98 | 3 | 12 |
| Bad Effects VAS | TEmax | A | 33 | 2.18 | 0.76 | 0.48 | 0.5 | 0.5 | 1.5 | 24 |
| Bad Effects VAS | TEmax | B | 33 | 2.20 | 0.43 | 0.48 | 0.5 | 1.5 | 3 | 12 |
| Bad Effects VAS | TEmax | E | 33 | 0.63 | 0.09 | 0.48 | 0.5 | 0.5 | 0.5 | 3 |
| Drug Liking VAS | Emax | C | 33 | 81.36 | 2.82 | 50 | 69 | 83 | 99 | 100 |
| Drug Liking VAS | Emax | D | 33 | 91.70 | 2.00 | 63 | 88 | 100 | 100 | 100 |
| Drug Liking VAS | Emax | A | 33 | 78.12 | 3.32 | 50 | 63 | 75 | 100 | 100 |
| Drug Liking VAS | Emax | B | 33 | 89.03 | 2.32 | 55 | 79 | 96 | 100 | 100 |
| Drug Liking VAS | Emax | E | 33 | 54.24 | 1.76 | 50 | 50 | 51 | 51 | 100 |
| Drug Liking VAS | Emin | C | 33 | 47.33 | 1.69 | 0 | 50 | 50 | 50 | 50 |
| Drug Liking VAS | Emin | D | 33 | 46.45 | 1.61 | 9 | 50 | 50 | 50 | 50 |
| Drug Liking VAS | Emin | A | 33 | 45.55 | 2.20 | 0 | 50 | 50 | 50 | 51 |
| Drug Liking VAS | Emin | B | 33 | 45.58 | 1.99 | 0 | 50 | 50 | 50 | 51 |
| Drug Liking VAS | Emin | E | 33 | 48.33 | 1.51 | 0 | 50 | 50 | 50 | 50 |
| Drug Liking VAS | TA_AUE | C | 33 | 55.86 | 2.42 | 6.45 | 51.54 | 53.16 | 56.08 | 98.74 |
| Drug Liking VAS | TA_AUE | D | 33 | 60.30 | 1.75 | 50.07 | 54.65 | 56.30 | 61.53 | 97.53 |
| Drug Liking VAS | TA_AUE | A | 33 | 55.83 | 1.75 | 39.13 | 51.17 | 53.05 | 56.85 | 97.34 |
| Drug Liking VAS | TA_AUE | B | 33 | 60.00 | 1.70 | 46.01 | 54.70 | 57.30 | 62.51 | 99.48 |
| Drug Liking VAS | TA_AUE | E | 33 | 49.90 | 0.50 | 34.32 | 50.00 | 50.02 | 50.46 | 53.19 |
| Drug Liking VAS | TEmax | C | 33 | 2.07 | 0.15 | 0.5 | 1.5 | 2 | 3 | 4 |
| Drug Liking VAS | TEmax | D | 33 | 2.00 | 0.36 | 0.5 | 1 | 1.5 | 2 | 12 |
| Drug Liking VAS | TEmax | A | 33 | 3.38 | 0.69 | 0.5 | 1.98 | 2.98 | 4 | 24 |
| Drug Liking VAS | TEmax | B | 33 | 2.67 | 0.38 | 1 | 1.5 | 2 | 3 | 12 |
| Drug Liking VAS | TEmax | E | 33 | 1.85 | 0.46 | 0.48 | 0.5 | 0.5 | 2 | 12 |
| Drug Liking VAS | TEmin | C | 33 | 2.92 | 1.05 | 0.48 | 0.5 | 0.5 | 1 | 24 |
| Drug Liking VAS | TEmin | D | 33 | 3.98 | 1.06 | 0.48 | 0.5 | 0.5 | 6 | 24 |
| Drug Liking VAS | TEmin | A | 33 | 2.10 | 0.80 | 0.48 | 0.5 | 0.5 | 1.5 | 24 |
| Drug Liking VAS | TEmin | B | 33 | 3.00 | 0.90 | 0.48 | 0.5 | 0.5 | 3 | 24 |
| Drug Liking VAS | TEmin | E | 33 | 2.03 | 0.84 | 0.48 | 0.5 | 0.5 | 0.5 | 24 |
| Good Effects VAS | Emax | C | 33 | 74.94 | 4.89 | 0 | 64 | 85 | 95 | 100 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Good Effects VAS | Emax | D | 33 | 89.48 | 2.33 | 49 | 82 | 96 | 100 | 100 |
| Good Effects VAS | Emax | A | 33 | 66.67 | 5.53 | 0 | 51 | 73 | 91 | 100 |
| Good Effects VAS | Emax | B | 33 | 88.97 | 3.00 | 11 | 81 | 96 | 100 | 100 |
| Good Effects VAS | Emax | E | 33 | 12.06 | 4.63 | 0 | 0 | 0 | 3 | 100 |
| Good Effects VAS | TA_AUE | C | 33 | 14.75 | 2.97 | 0.00 | 4.41 | 9.32 | 19.59 | 74.47 |
| Good Effects VAS | TA_AUE | D | 33 | 24.09 | 2.60 | 3.16 | 12.12 | 19.31 | 33.61 | 71.06 |
| Good Effects VAS | TA_AUE | A | 33 | 14.35 | 3.32 | 0.00 | 4.57 | 8.23 | 15.21 | 84.59 |
| Good Effects VAS | TA_AUE | B | 33 | 23.83 | 3.08 | 0.70 | 11.28 | 23.64 | 30.55 | 98.70 |
| Good Effects VAS | TA_AUE | E | 33 | 2.99 | 1.64 | 0.00 | 0.00 | 0.00 | 0.09 | 50.18 |
| Good Effects VAS | TEmax | C | 33 | 1.86 | 0.12 | 0.5 | 1.5 | 1.98 | 2 | 3.02 |
| Good Effects VAS | TEmax | D | 33 | 1.65 | 0.19 | 0.5 | 1 | 1.5 | 1.52 | 6 |
| Good Effects VAS | TEmax | A | 33 | 2.32 | 0.23 | 0.48 | 1.48 | 2 | 3 | 6 |
| Good Effects VAS | TEmax | B | 33 | 2.37 | 0.26 | 1 | 1.5 | 2 | 3 | 8 |
| Good Effects VAS | TEmax | E | 33 | 1.03 | 0.21 | 0.48 | 0.5 | 0.5 | 0.5 | 6 |
| High VAS | Emax | C | 33 | 67.27 | 4.89 | 0 | 50 | 74 | 87 | 100 |
| High VAS | Emax | D | 33 | 88.76 | 2.66 | 38 | 80 | 97 | 100 | 100 |
| High VAS | Emax | A | 33 | 60.52 | 5.75 | 0 | 50 | 65 | 89 | 100 |
| High VAS | Emax | B | 33 | 85.82 | 3.12 | 9 | 82 | 90 | 100 | 100 |
| High VAS | Emax | E | 33 | 10.00 | 3.83 | 0 | 0 | 0 | 0 | 66 |
| High VAS | TA_AUE | C | 33 | 11.09 | 2.05 | 0 | 3 | 8.27 | 16.83 | 57.42 |
| High VAS | TA_AUE | D | 32 | 19.89 | 2.10 | 1.88 | 8.69 | 18.44 | 27.96 | 48.81 |
| High VAS | TA_AUE | A | 33 | 10.42 | 2.19 | 0.00 | 3.29 | 6.58 | 11.71 | 57.29 |
| High VAS | TA_AUE | B | 33 | 19.68 | 2.26 | 0.56 | 9.78 | 18.93 | 26.22 | 66.00 |
| High VAS | TA_AUE | E | 33 | 1.13 | 0.63 | 0 | 0 | 0 | 0 | 19.49 |
| High VAS | TEmax | C | 33 | 1.94 | 0.11 | 0.5 | 1.5 | 2 | 2 | 3.02 |
| High VAS | TEmax | D | 33 | 1.77 | 0.15 | 1 | 1 | 1.5 | 2 | 4 |
| High VAS | TEmax | A | 33 | 2.45 | 0.25 | 0.48 | 1.5 | 2 | 3.98 | 6 |
| High VAS | TEmax | B | 33 | 2.49 | 0.18 | 1 | 2 | 2.07 | 3 | 6 |
| High VAS | TEmax | E | 33 | 0.86 | 0.14 | 0.48 | 0.5 | 0.5 | 0.5 | 3 |
| Overall Drug Liking | Emax | C | 33 | 81.00 | 3.71 | 0 | 74 | 86 | 100 | 100 |
| Overall Drug Liking | Emax | D | 33 | 84.82 | 2.98 | 26 | 77 | 86 | 100 | 100 |
| Overall Drug Liking | Emax | A | 33 | 77.70 | 3.45 | 50 | 61 | 80 | 100 | 100 |
| Overall Drug Liking | Emax | B | 33 | 87.48 | 2.71 | 50 | 77 | 95 | 100 | 100 |
| Overall Drug Liking | Emax | E | 33 | 52.36 | 1.68 | 33 | 50 | 50 | 51 | 100 |
| Overall Drug Liking | Emin | C | 33 | 75.85 | 3.69 | 0 | 64 | 80 | 90 | 100 |
| Overall Drug Liking | Emin | D | 33 | 77.03 | 4.23 | 0 | 67 | 80 | 99 | 100 |
| Overall Drug Liking | Emin | A | 33 | 73.45 | 3.95 | 14 | 51 | 72 | 100 | 100 |
| Overall Drug Liking | Emin | B | 33 | 76.39 | 3.76 | 18 | 58 | 80 | 98 | 100 |
| Overall Drug Liking | Emin | E | 33 | 50.03 | 2.47 | 0 | 50 | 50 | 51 | 100 |
| Stoned VAS | Emax | C | 33 | 55.94 | 5.75 | 0 | 27 | 63 | 80 | 100 |
| Stoned VAS | Emax | D | 33 | 84.39 | 3.64 | 10 | 73 | 95 | 100 | 100 |
| Stoned VAS | Emax | A | 33 | 53.00 | 6.36 | 0 | 12 | 65 | 85 | 100 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Stoned VAS | Emax | B | 33 | 81.09 | 4.67 | 10 | 82 | 91 | 100 | 100 |
| Stoned VAS | Emax | E | 33 | 5.03 | 2.77 | 0 | 0 | 0 | 0 | 67 |
| Stoned VAS | TA_AUE | C | 33 | 9.39 | 1.78 | 0.00 | 1.33 | 5.39 | 16.08 | 43.30 |
| Stoned VAS | TA_AUE | D | 32 | 18.67 | 2.05 | 0.21 | 8.48 | 17.71 | 27.17 | 48.70 |
| Stoned VAS | TA_AUE | A | 33 | 8.93 | 1.85 | 0.00 | 0.58 | 6.13 | 9.41 | 50.79 |
| Stoned VAS | TA_AUE | B | 33 | 18.40 | 2.02 | 0.38 | 10.33 | 18.99 | 26.01 | 47.31 |
| Stoned VAS | TA_AUE | E | 33 | 0.85 | 0.61 | 0.00 | 0.00 | 0.00 | 0.00 | 19.34 |
| Stoned VAS | TEmax | C | 33 | 1.77 | 0.13 | 0.5 | 1.5 | 1.98 | 2 | 3.02 |
| Stoned VAS | TEmax | D | 33 | 1.91 | 0.19 | 0.5 | 1.48 | 1.5 | 2 | 6 |
| Stoned VAS | TEmax | A | 33 | 2.22 | 0.27 | 0.48 | 1.48 | 2 | 3 | 6 |
| Stoned VAS | TEmax | B | 33 | 2.48 | 0.20 | 1.00 | 1.5 | 2 | 3 | 6 |
| Stoned VAS | TEmax | E | 33 | 0.86 | 0.19 | 0.48 | 0.5 | 0.5 | 0.5 | 6 |
| SDV ($) | Emax | C | 33 | 18.35 | 2.47 | 0.25 | 9 | 13.75 | 26.75 | 48 |
| SDV ($) | Emax | D | 33 | 26.80 | 2.63 | 5 | 15 | 26.75 | 40.75 | 48 |
| SDV ($) | Emax | A | 33 | 17.82 | 2.67 | 0.25 | 5.5 | 15 | 26.75 | 48 |
| SDV ($) | Emax | B | 33 | 25.20 | 2.70 | 0.25 | 12.75 | 26.75 | 40.75 | 48 |
| SDV ($) | Emax | E | 33 | 1.36 | 0.62 | 0.25 | 0.25 | 0.25 | 0.25 | 15 |
| Take Drug Again VAS | Emax | C | 33 | 79.27 | 5.57 | 0 | 76 | 93 | 100 | 100 |
| Take Drug Again VAS | Emax | D | 33 | 84.58 | 3.31 | 20 | 75 | 88 | 100 | 100 |
| Take Drug Again VAS | Emax | A | 33 | 69.79 | 6.56 | 0 | 40 | 89 | 100 | 100 |
| Take Drug Again VAS | Emax | B | 33 | 86.79 | 3.20 | 25 | 80 | 97 | 100 | 100 |
| Take Drug Again VAS | Emax | E | 33 | 10.39 | 4.39 | 0 | 0 | 0 | 0 | 100 |

[1] Alertness/Drowsiness=Alertness/Drowsiness VAS (bipolar); Overall Drug Liking=Overall Drug Liking VAS (bipolar); SDV= Subjective Drug Value

[2] TA_AUE = time-adjusted AUE (area under the effect curve from first to last timepoint using linear trapezoidal rule divided by time between first and last timepoints). TEmax and TEmin were expressed in hour.

[3] TRT= Treatment; A=Marinol 10 mg; B=Marinol 30 mg; C=Dronabinol Oral Solution 10 mg; D=Dronabinol Oral Solution 30 mg; E=placebo

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

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/s/

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WEI LIU
12/18/2015

QIANYU DANG
12/18/2015

YI TSONG
01/04/2016