CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205525Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Memo

NDA:	205525
Generic Name:	Dronabinol oral solution
Route of administration	Oral solution (4.25 mg/0.85 ml)
Indication:	Anti-emetic
Submission Type:	Consult from DGIEP
Priority Classification:	Standard
Submission Date to DPP:	3/23/16
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen Balimane, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Executive Summary

NDA 205525 is a 505(b)(2) application for dronabinol oral solution (4.25 mg/0.85 ml) co-packaged with a dosing syringe for (a) treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and b) anorexia associated with weight loss in patients with AIDS. Dronabinol oral solution is a new formulation of dronabinol, and contains synthetic delta-9-tetrahydrocannabinol (delta-9-THC).

DGIEP sent a consult to DPP with the following questions which have been addressed below:

> Q1: Is there a real DDI between dronabinol and fluoxetine that results in an increased risk of mania/hypomania when the two are used together, beyond the risk with fluoxetine alone? If this is a true DDI, please provide proposed wording in the W&P about this risk.

Based on the review of the labels as well as literature data [1-3], fluoxetine and dronabinol have different pathways of metabolism. Fluoxetine is a potent inhibitor of CYP2D6 and also undergoes extensive hepatic metabolism mainly via CYP2D6 pathway [2]. Dronabinol is known to be metabolized primarily via the CYP2C9, 2C19 and 3A4 pathways [3]. Based on literature evidence, it is unclear whether dronabinol is a CYP2D6 inhibitor or not. Though they do not share the same CYP-based metabolic pathway, comprehensive literature data does not exist for all the detailed Phase 2 metabolism pathways as well as transporter pathways for the two drugs. Thus, though the risk for a PK-based drug-drug interaction is low between dronabinol and fluoxetine, it cannot be completely ruled-out.

> Q2: Is the risk specific to fluoxetine or is it applicable to other drugs that are used to treat MDD or OCD. If possible, please cite other examples

We believe that the potential pharmacodynamics interaction between dronabinol oral solution and fluoxetine would be best addressed by the Division of Anesthesia, Analgesia and Addiction Products given their expertise with the cannabinoids.

References:

1. *MARINOAL© label*
2. *PROZAC© label*
3. *Chem Biodivers. 2007 August ; 4(8): 1770–1804*

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/s/

PRAVEEN BALIMANE
04/27/2016

HAO ZHU
04/27/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205525	Submission Date(s): 06/01/2015, 09/28/2015, 11/30/2015, 12/01/2015, 01/15/2016
Brand Name	SYNDROS
Generic Name	Dronabinol
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Insys Therapeutics, Inc.
Relevant IND(s)	75228
Submission Type; Code	Resubmission after RTF; 505b(2) NDA
Formulation; Strength(s)	Oral solution; 5 mg/mL or 4.25 mg in 0.85 mL
Indication	For the treatment of nausea and vomiting associated with cancer chemotherapy and anorexia associated with weight loss in patients with AIDS

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1 Executive Summary

1.1 Recommendation

NDA 205525, for dronabinol oral solution is acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

This is a resubmission of a 505 b (2) NDA for new dronabinol oral solution formulation. The NDA references the approved drug, Marinol® dronabinol capsule (NDA 018651) as listed drug. Four BA studies (2 pivotal and 2 pilot) and six articles published in the literature were reviewed to support the approval of this NDA.

Relative bioavailability (proposed product vs. Marinol capsule) under fasted dosing conditions

Parent drug, dronabinol (delta9-tetrahydrocannabinol): In healthy volunteers under fasted dosing conditions, the proposed dronabinol oral solution at a dose of 4.25 mg (in 0.85 mL) provided bioequivalent systemic exposures (Cmax, AUCt and AUCinf) of parent dronabinol (delta9-THC) compared to approved Marinol capsule 5 mg.

Active metabolite (11-hydroxy-delta9-THC): The active metabolite exposures were comparable following the test solution (4.25 mg) and reference capsule (5 mg), although bioequivalence was not strictly met for this analyte. This is considered not critical as the dose is titrated to effect for both of the proposed indications.

Relative bioavailability (proposed product vs. Marinol capsule) under fed dosing conditions

Parent dronabinol (delta9-tetrahydrocannabinol): In healthy volunteers, under fed dosing conditions, the proposed dronabinol oral solution (4.25 mg), demonstrated comparable AUC values to the reference approved Marinol capsule (5 mg). Cmax following the test formulation was ~ 40 % lower relative to Cmax of the reference product under fed conditions.

Active metabolite (11-hydroxy-delta9-THC): Under fed conditions, the AUC values of the active metabolite for the test solution were comparable to those from Marinol capsule, although the Cmax was ~ 40% lower for the test formulation.

Food-effect on bioavailability

Parent dronabinol (delta9-tetrahydrocannabinol): The reference Marinol label doesn't contain information regarding food-effect on PK. In the fed BA study conducted under this NDA, a significant food-effect (fed vs. fasted exposure comparison) on the bioavailability of parent dronabinol (delta9-THC) can be concluded for both the test and reference formulations. For the proposed drug product under fed conditions, although the Cmax values appeared to be lower by 22 %, the AUC of dronabinol increased by ~ 280 % (or 2.8-fold) (cross-study comparison), respectively, for the proposed product. The Cmax and AUC values increased by 6 % and 280%, respectively, for the reference product under fed dosing (within-study comparison). In addition, the median Tmax values were prolonged for approximately 4.5 hours for the test formulation and 3.5 h for the reference formulation under fed conditions.

Active metabolite (11-hydroxy-delta9-THC): The test and reference formulation data also suggested a food-effect on metabolite PK, with a decrease in Cmax by ~ 33 % and an increase in AUC by ~ 40 % under fed conditions for the reference product. For the test formulation, a cross-study comparison suggested a decrease in Cmax of the active metabolite by ~ 55 % and an increase in AUC by ~ 19 % under fed conditions.

Metabolism

To update the labeling with recent information, 2 published documents were primarily reviewed to identify the primary enzymes responsible for the metabolism of dronabinol and address potential for enzyme polymorphism. Published data suggests that dronabinol is primarily metabolized by CYP2C9 and CYP3A4. CYP2C9 appears to be the enzyme responsible for the formation of the principle active metabolite, 11-hydroxy-delta9-THC. In addition, literature suggests that a 2-3 fold higher dronabinol exposure can be noted in individuals carrying genetic variants associated with diminished CYP2C9 function.

DDI potential

To update the labeling with recent information on drug interaction potential of dronabinol, four published papers were primarily reviewed and information was summarized in the labeling:

(b) (4)

Effect of other drugs on dronabinol PK: Dronabinol is primarily metabolized by CYP2C9 and CYP3A4 enzymes. Inhibitors of these enzymes may increase, while inducers may decrease, the systemic exposure of the drug and/or active metabolite. (b) (4) or loss of efficacy of SYNDROS. Monitor (b) (4) for

increased adverse reactions [redacted] inhibitors of CYP2C9 [e.g. Amiodarone, fluconazole [redacted] and inhibitors of CYP3A4 enzymes [e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, erythromycin, grapefruit juice [redacted]

Labeling implications

The revised dosing recommendations take into consideration that a lower dose of dronabinol oral solution (4.25 mg in 0.85 mL) achieves systemic exposures provided by approved Marinol 5 mg capsule. In addition, due to the food-effect on PK with a lower Cmax and a delayed Tmax, it is recommended that the first dose for the anti-emetic indication should be taken on an empty stomach at least 30 minutes before eating. Because food can substantially change the systemic exposure to dronabinol and its active metabolite, the timing of dosing in relation to meal times should be kept consistent for each chemotherapy cycle, once the dosage has been determined from the titration process.

Inspections:

In a memo in DARRTs dated 08/12/2015, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data for the pivotal bioequivalence trials in NDA 205525 without an on-site inspection. The rationale was that OSIS recently inspected the clinical and bioanalytical sites. The inspectional outcome from the inspections was classified as No Action Indicated.

2 Summary of CPB Findings

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

This is a resubmission of a 505 b(2) NDA for new dronabinol oral solution formulation. The NDA references the approved drug, Marinol® dronabinol capsule USP (NDA 018651; approved on May 31, 1985) as listed drug. The original submission dated August 12, 2014 received a refuse-to-file on October 10, 2014 citing 'failure to address the requirements under the pediatric research equity act" as the sponsor did not have an agreed initial pediatric study plan (iPSP) prior to NDA submission. Prior to this resubmission, sponsor received an agreed iPSP letter on May 19, 2015 under IND 75228.

What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The chemical name of dronabinol, a synthetic delta-9-tetrahydrocannabinol (delta-9-THC) is (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. The molecular weight of dronabinol is 314.46 g/mol and its molecular formula is $C_{21}H_{30}O_2$. Delta-9-tetrahydrocannabinol is also a naturally occurring component of Cannabis sativa L. (Marijuana). Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7. Dronabinol has the following structural formula:

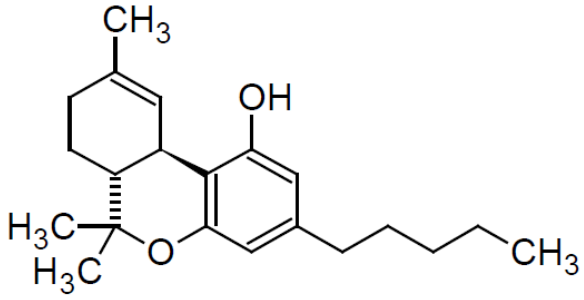


Figure 1: Structure of dronabinol

The proposed dronabinol oral solution is filled in a clear, amber-colored glass bottle with a fill volume of 30 mL containing 150 mg drug (5 mg/mL). The solution is co-packaged with an oral dosing syringe marked with the graduations allowing the measurement of prescribed doses. Quantitative and qualitative composition of the drug product is presented in Table 1.

Table 1: Composition of Dronabinol Oral Solution

Component	Quality Standard	Function	Composition	
			%, (w/w)	mg/ mL
Dronabinol	USP	Active Ingredient	0.541	5.00
Butylated hydroxyanisole (BHA)	NF	(b) (4)	0.010	0.09
Sucralose	NF	Sweetener	0.050	0.46
Methyl paraben	NF	Preservative	0.020	0.18
Propyl paraben	NF	Preservative	0.020	0.18
PEG 400	NF[b]	Co-solvent	12.000	110.91
Propylene glycol	USP	Co-solvent	5.500	50.83
Water	USP	Solvent/Diluent	31.859	294.45
Dehydrated alcohol	USP	Co-solvent	QS to 100.000 % (corresponds to about 50.000%)	QS to 1.00 mL (corresponds to about 462.11 mg)
(b) (4)				
Total	-	-	100.000%	1.00 mL

What are the proposed mechanism of action and therapeutic indications? What are the proposed dosages and route of administration?

Dronabinol Oral Solution contains a synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Dronabinol is an orally active cannabinoid that has many effects on the central nervous system, including sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues and may play a role in mediating the effects of dronabinol and other cannabinoids.

Similar to the approved Marinol capsule, dronabinol oral solution is proposed for the treatment of:
1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

As noted in the executive summary and in the pivotal bioequivalence trial results in this review, 4.25 mg of dronabinol in 0.85 mL of the proposed oral solution provides systemic exposure comparable to a 5 mg dose of dronabinol from the approved Marinol capsule (reference). Thus doses are proposed for the new formulation after taking this difference into consideration, so as to provide comparable exposures to approved doses of Marinol capsules:

- Anorexia: A starting dose of (b) (4) (2.125 mg) taken twice daily, 1 h before lunch and supper is recommended. Note that the dose in these patients can be

gradually titrated up to a maximum dose of (b) (4) (8.5 mg) twice daily to achieve adequate therapeutic effect.

- Anti-emetic: A starting dose of 4.25 mg/m2 given 1-3 h prior to chemotherapy, then every 2 to 4 h after chemotherapy is given, for a total of 4 to 6 doses/day is recommended. Note that the dose in these patients can be titrated up to achieve adequate clinical response, as tolerated in increments of (b) (4) mg/m2 up to a maximum dose of 12.75 mg/m2 per dose for 4 to 6 doses per day.

What are the design features of the clinical pharmacology, biopharmaceutics studies used to support dosing or claims?

The dronabinol oral solution development included studies evaluating the tolerability, pharmacokinetics and relative bioavailability *vs*. Marinol (listed drug) in healthy subjects:

- INS-12-015, a pivotal 4-period replicate, single-dose, randomized crossover study of the comparative bioavailability of Dronabinol Solution 4.25 mg and Marinol® 5 mg capsules
- INS004-15-059, an Open-Label, Randomized, Single-Dose, Six-Sequence, Three-Period, Crossover Comparative Bioavailability Study of Dronabinol Oral Solution, 4.25 mg under Fed Conditions, and Marinol Capsule, 5 mg under Fed and Fasted Conditions in Healthy Volunteers

- INS-06-006, a Phase I, placebo-controlled, single-blind study to compare the relative bioavailability of ascending doses of Dronabinol Syrup (5 mg/mL)
- INS-08-008, a pilot study to compare the pharmacokinetic profile and comparative bioavailability of two dronabinol test formulations, Dronabinol Syrup 10 mg and Dronabinol Oral Solution 10 mg, and Marinol® Capsules 10 mg
- INS-10-012, a 4-period replicate, single-dose, randomized crossover study of the comparative bioavailability of Dronabinol Oral Solution 5 mg and Marinol® 5 mg capsules

Of these, trials INS-12-015 and INS004-15-059 are the key studies for evaluating the approvability of this new formulation and therefore will be the primary focus of this review. Studies INS08-008 and INS10-012 were also reviewed (see appendices). In addition, the bioanalytical method validation and assay reports, as well as proposed labeling were reviewed in detail. Active metabolite PK and comparative bioavailability information was included in the submission and was reviewed, in relation to the metabolite PK of the listed drug. In addition, to update the metabolism and drug interaction section of the proposed labeling, six literature references were reviewed.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Plasma dronabinol and active metabolite were assayed using a validated LC-MS/MS method. The assay procedure was found to be linear over the range of 0.025 - 10 ng/mL for both the analytes. The performance of calibration standards, QCs, and results of the incurred sample reproducibility test for each clinical trial were within acceptable ranges.

Is the proposed dronabinol formulation (4.25 mg oral solution) bioequivalent to the reference dronabinol (Marinol 5 mg capsule) formulation?

Bioequivalence conclusions: Yes, bioequivalence (BE) of dronabinol systemic exposure has been demonstrated for the test formulation (oral solution) at a dose of 4.25 mg and the reference formulation (Marinol capsule) at a dose of 5 mg, under fasted conditions of dosing.

Study details: Study INS-12-015 was a single dose, open-label, randomized, four-period, two -treatment, two-sequence, replicate design, crossover study in 52 healthy male and female adult volunteers (18-53 years of age). Subjects received each treatment twice [i.e. replicates of test (dronabinol oral solution; 4.25 mg in 0.85 mL) or reference (Marinol capsules; 5 mg)] in the four study periods and were randomly assigned to one of the two sequences (TRTR or RTRT). There was a washout of 7 d between the periods. Dosing was done at a pre-specified time each morning, under fasted conditions. Serial plasma samples were obtained for up to 48 h post-dose.

Pivotal BE study INS-12-015: Pharmacokinetics of parent drug (dronabinol)

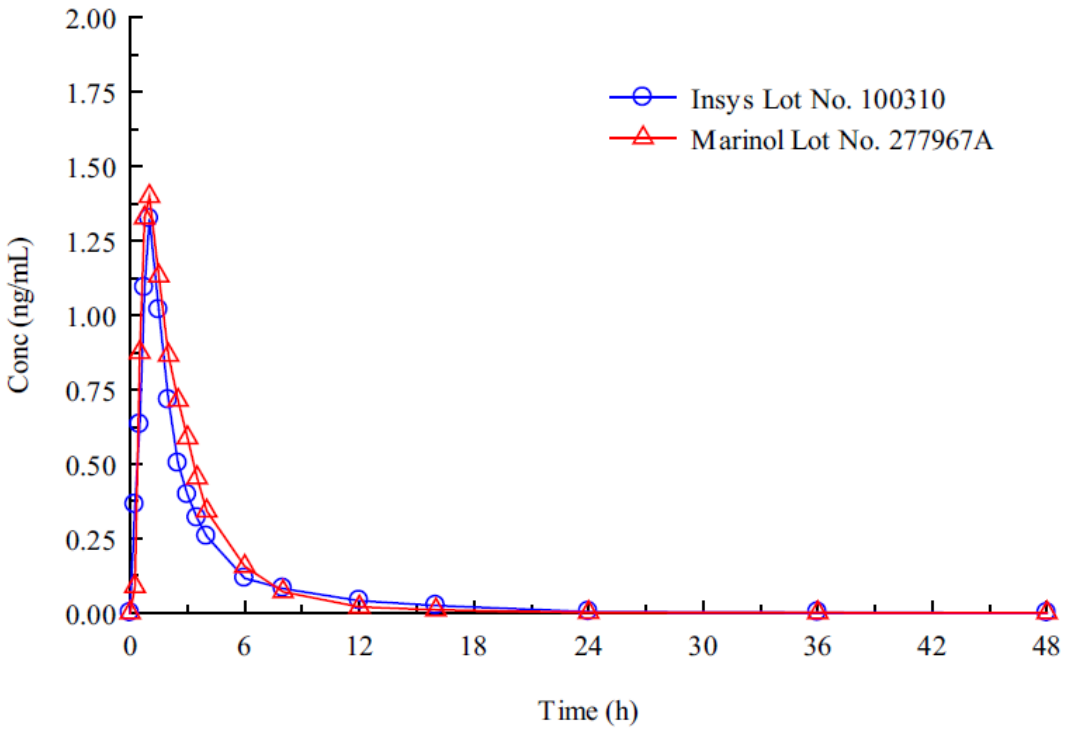


Figure 2: Mean plasma concentrations of dronabinol with replicates combined after oral administration of a single dose of Dronabinol Solution 4.25 mg and of Marinol Capsule 5 mg to healthy volunteers under fasted conditions.

Table 2: PK summary for dronabinol

Summary of PK parameters for dronabinol with replicates combined after oral administration of a single dose of Dronabinol Solution 4.25 mg and of Marinol Capsule 5 mg to healthy volunteers under fasted conditions.

Parameter*	Insys Lot No. 100310 (Test)	Marinol Lot No. 277967A (Reference)
Cmax (ng/mL)	1.95 ± 1.28 (101)	2.41 ± 1.60 (101)
Tmax (h)	1.00 (101) [0.50 – 4.00]	1.50 (101) [0.50 – 6.00]
AUC(0-t) (h×ng/mL)	3.53 ± 1.87 (101)	3.99 ± 2.51 (101)
AUC(inf) (h×ng/mL)	3.84 ± 1.80 (91)	4.05 ± 2.50 (86)
λz (1/h)	0.1488 ± 0.0675 (91)	0.3271 ± 0.1555 (86)
t½ (h)	5.58 ± 2.66 (91)	3.07 ± 2.64 (86)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Statistical findings: Reference-scaled BE analyses was used as the within subject PK variability (sWR) for reference drug exceeded 0.294 with regard to all three PK parameters. The bioequivalence criteria were met i.e. test to reference geometric mean ratios (GMR) were within 0.8-1.25 and the criteria bounds were less than zero for the three PK parameters tested. Hence the analysis supports bioequivalence of the test and reference dronabinol products with respect to parent dronabinol, under fasted conditions.

Table 3: Statistical summary for the parent drug (dronabinol; delta9-THC)

Parameter	T/R Ratio	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.95	0.1886051	0.4342869	-0.103484	Scaled/PE	PASS
LAUCI	0.93	0.2107749	0.4591023	-0.102459	Scaled/PE	PASS
LCMAX	0.83	0.4232008	0.6505388	-0.176975	Scaled/PE	PASS

Pivotal BE study INS-12-015: Pharmacokinetics of active metabolite

Table 4: PK summary for the active metabolite

Summary of PK parameters for 11-OH-Δ9-THC with replicates combined after oral administration of a single dose of Dronabinol Solution 4.25 mg and of Marinol Capsule 5 mg to healthy volunteers under fasted conditions.

Parameter*	Insys Lot No. 100310 (Test)	Marinol Lot No. 277967A (Reference)
Cmax (ng/mL)	2.77 ± 1.48 (101)	3.63 ± 2.19 (101)
Tmax (h)	1.50 (101) [0.50 – 4.00]	1.50 (101) [0.50 – 6.00]
AUC(0-t) (h×ng/mL)	10.6 ± 5.13 (101)	12.9 ± 6.67 (101)
AUC(inf) (h×ng/mL)	11.2 ± 5.33 (97)	13.8 ± 6.88 (97)
λz (1/h)	0.0716 ± 0.0452 (97)	0.0708 ± 0.0583 (97)
t½ (h)	11.7 ± 4.01 (97)	11.9 ± 3.89 (97)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Statistical findings: BE analysis was conducted for the active metabolite 11-hydroxy delta9-THC, as supportive information. As the within-subject PK variability (sWR) for this analyte following the reference Marinol was < 0.294 for all PK parameters, average BE analysis was employed by the sponsor. The absence of high variability in metabolite PK (i.e. sWR < 0.294) was verified by the reviewer analysis as well using SAS 9.3.

For the active metabolite, the PK parameters failed average bioequivalence criteria modestly in that, the lower 90 % confidence bounds for exposure parameters fell somewhat below the lower regulatory BE threshold of 80 %. Given the modest differences in metabolite exposure from the test solution relative to Marinol capsule, and given that doses are titrated to effect for both indications, this finding doesn't appear to be clinically meaningful.

Table 5: Statistical summary for active metabolite in pivotal trial INS-12-015

	Least Squares Geometric Means		Geometric Mean Ratio (%)*				Within-Subject Standard Deviation†	
	Insys	Marinol					Insys	Marinol
Parameter	Lot No. 100310	Lot No. 277967A	Estimate	90% Confidence Interval			Lot No. 100310	Lot No. 277967A
Insys Lot No. 100310 vs. Marinol Lot No. 277967A								
Cmax	2.36	3.05	77.33	72.50	→	82.49	0.287	0.265
AUC(0-t)	9.05	10.90	82.97	77.98	→	88.28	0.214	0.218
AUC(inf)	9.67	11.53	83.92	79.02	→	89.11	0.194	0.218

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In the original NDA submission, the sponsor did not provide a food effect or fed BA/BE study. During the review of this NDA, a food effect study of a particular design was requested of the sponsor as explained below

The test dronabinol solution is proposed for both indications labeled for Marinol capsule i.e. treatment of anorexia in AIDS patients and chemotherapy related nausea and vomiting in patients refractory to other therapies. The sponsor has established comparable exposures of their test solution to reference only under fasted conditions. The Marinol product label is silent with regard to food-effect on bioavailability, clinical trial design with regard to food, as well as dosing instructions with regard to food intake. Labeling the anorexia indication for the new formulation was straight forward, as the doses need to be taken 1 hour prior to meals twice daily and thus food effect is not important for this indication. However, for the nausea and vomiting indication, the dose was to be administered up to 4 to 6 times a day and therefore requiring fasted dosing (for which we had relative bioavailability data) was unlikely to be a practical recommendation. Thus the sponsor was requested to address this issue to adequately label the solution for both indications. While a food-effect BA study would normally be sufficient for a 505 b(2) submission, because food-effect information was absent for the reference formulation, a different design was recommended as described further below (i.e. BA of the test formulation under fed, relative to fed Marinol, and fasted Marinol). The third group (i.e. fasted Marinol) was incorporated into the design in case the fed BA findings for the test vs. reference suggested different exposures. Having data from the Marinol fasted arm would allow determination if the exposures still fall within those noted for Marinol under fasted and fed conditions, as it appears that currently Marinol can be taken without regard to meals.

Food effect conclusions: Dosing under fed conditions markedly increased the systemic exposure (AUC values) of dronabinol and delayed the peak concentrations for both the test oral solution and the reference capsule formulations, compared to fasted dosing. Under fed conditions, the Cmax for dronabinol from the test solution was lower compared to reference Marinol by ~ 40 %. Under fed conditions, the parent/active metabolite ratio was closer to 1, while metabolite exposure was approximately 3-fold greater to that of parent in fasted conditions.

Food effect labeling implications:

Because food delays the absorption of dronabinol from SYNDROS, administer the first dose on an empty stomach, at least 30 minutes before eating. Subsequent doses can be taken without regard to meals.

Because food can substantially change the systemic exposure to dronabinol and its active metabolite, the timing of dosing in relation to meal times should be kept consistent for each chemotherapy cycle, once the dosage has been determined from the titration process.

Food effect Study details: Study INS004-15-059 was an open-label, randomized, single-dose, 6-sequence, 3-period, crossover comparative bioavailability study of

dronabinol oral solution, 4.25 mg under fed conditions and Marinol (reference) capsule, 5 mg under fed and fasted conditions in healthy volunteers (18-50 years of age, inclusive). Each treatment was separated by a 7-day washout period. During treatments A and B, subjects received the high-fat, high-calorie breakfast beginning 30 minutes prior to scheduled administration of the dose and ending within 5 minutes prior to dosing. PK sampling was done for 48 hours post-dose. Treatments were not replicated in this study, and conventional (average) bioequivalence analyses were used to obtain relative bioavailability estimates across various treatments:

• Treatment A: Dronabinol oral solution, 4.25 mg, administered under fed conditions
• Treatment B: Marinol (dronabinol) Capsule, 5 mg, administered under fed conditions
• Treatment C: Marinol (dronabinol) Capsule, 5 mg, administered under fasted conditions

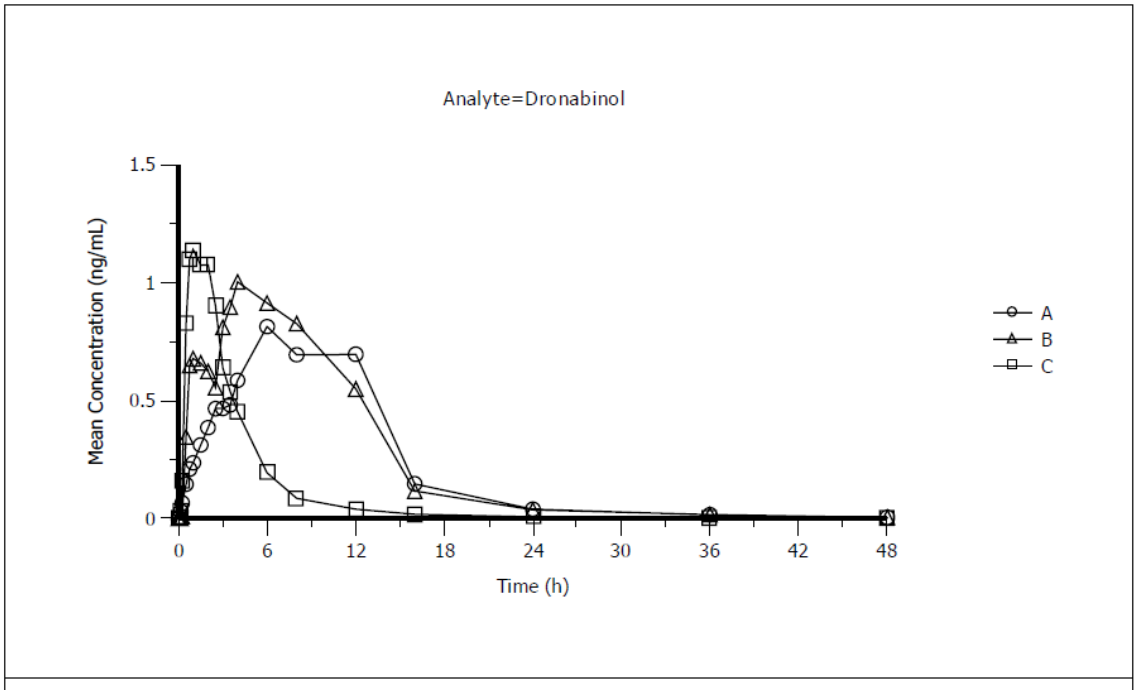


Figure 3: Mean dronabinol concentration-time profiles after test oral solution, 4.25 mg under fed conditions (treatment A), and Marinol capsule, 5 mg under fed (Treatment B) and fasted conditions (Treatment C).

Table 6: Pharmacokinetics of dronabinol (the parent compound)

Mean ± SD	Test solution (fed)	Marinol (fed)	Marinol (fasted)
Cmax (ng/mL)	1.52 ± 0.97	2.60 ± 1.74	2.19 ± 1.06
Tlag (h) Median [Range]	0.16 [0 – 0.25]	2.0 [0.16 – 6.0]	0.5 [0.08 -3.0]
Tmax (h) Median [Range]	6.0 [1.5 -12.0]	5.0 [0.5 -12.0]	1.5 [0.5 – 12.0]
AUC0-t (ng.h/mL)	9.10 ± 3.84	10.47 ± 4.85	4.44 ± 2.6
AUCinf (ng.h/mL)	10.25 ± 3.78	12.21 ± 4.83	4.33 ± 2.49
Half- life (h)	9.3 ± 6.7	10.4 ± 9.2	4.8 ± 5.8

Relative bioavailability comparisons for parent dronabinol:

Table 7: Solution-fed (test) vs. Marinol fed (reference)

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	60.80	51.99	71.10
AUCT	88.93	79.08	100.00
AUCINF	81.93	69.04	97.24
Test: Solution-fed; Reference: Marinol-fed			

Table 8: Solution-fed (test) vs. Marinol fasted (reference)

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	64.89	55.46	75.93
AUCT	219.14	194.82	246.50
AUCINF	236.61	201.95	277.22
Test: Solution-fed; Reference: Marinol-fasted			

Table 9: Marinol fasted vs. fed

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	106.73	91.36	124.69
AUCT	246.43	219.31	276.90
AUCINF	288.78	248.18	336.03
Test: Marinol-fed; Reference: Marinol-fasted			

Table 10: Pharmacokinetics of active metabolite 11-OH-delta9-THC

	Test solution (fed)	Marinol (fed)	Marinol (fasted)
Cmax (ng/mL)	1.23 ± 0.60	2.16 ± 1.50	3.12 ± 1.67
Tlag (h) Median [Range]	0.17 [0.08 – 0.5]	1.5 [0.16 – 4.0]	0.25 [0.08 – 3.0]
Tmax (h) Median [Range]	8.0 [2.0 – 16.0]	6.0 [0.75 – 12.4]	1.5 [0.75 – 6.0]
AUC0-t (ng.h/mL)	12.61 ± 5.10	14.84 ± 6.49	11.17 ± 6.07
AUCinf (ng.h/mL)	13.29 ± 5.23	15.59 ± 6.67	11.81 ± 6.18
Half-life (h)	11.2 ± 3.0	11.1 ± 3.0	12.5 ± 4.3

Relative bioavailability comparisons for the active metabolite:

Table 11: Metabolite PK: Dronabinol solution (test) vs. Marinol capsule (reference) under fed conditions

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	61.75	54.96	69.39
AUCT	85.69	80.24	91.51
AUCINF	86.16	80.96	91.70
Test: Solution-fed; Reference: Marinol-fed			

Table 12: Metabolite PK: Dronabinol solution (fed) vs. Marinol capsule (fasted)

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	41.62	37.03	46.77
AUCT	121.08	113.37	129.32
AUCINF	119.79	112.55	127.50
Test: Solution-fed; Reference: Marinol-fasted			

Table 13: Metabolite PK: Reference Marinol capsule fed vs. fasted

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	67.39	60.03	75.67
AUCT	141.31	132.38	150.83
AUCINF	139.03	130.69	147.90
Test: Marinol-fed; Reference: Marinol-fasted			

3 Labeling recommendations: See the final language in the approved labeling

Dosing and administration: Taking into consideration that a lower dose of the oral solution (4.25 mg in 0.85 mL) provides comparable systemic exposure to the approved Marinol capsule (5 mg), and considering the effect of food on PK, especially a delayed Tmax, the following dosing instructions are recommended for the proposed indications:

AIDS related anorexia indication:
The recommended adult starting dosage is (b) (4) (2.125 mg) orally twice daily, one hour before lunch and one hour before supper. If tolerated and further therapeutic effect is desired, the dosage may be increased gradually to (b) (4) (2.125 mg) one hour before lunch and (b) (4) (4.25 mg) one hour before supper. The dose may be further increased to (b) (4) (4.25 mg) one hour before lunch and (b) (4) (4.25 mg) one hour before supper, as tolerated to achieve a therapeutic effect. Maximum dosage (b) (4) (8.5 mg) twice daily (b) (4).

Chemotherapy related anti-emetic indication:
The recommended starting dosage is [redacted] (4.25 mg/m2) orally administered 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial effect, as tolerated to achieve a clinical effect, in increments of [redacted] (2.125 mg/m2). The maximum dosage is [redacted] (12.75 mg/m2) per dose for 4 to 6 doses per day.

Because food delays the absorption of dronabinol from SYNDROS, administer the first dose on an empty stomach, at least 30 minutes before eating. Subsequent doses can be taken without regard to meals.

Because food can substantially change the systemic exposure to dronabinol and its active metabolite, the timing of dosing in relation to meal times should be kept consistent for each chemotherapy cycle, once the dosage has been determined from the titration process.

Clinical Pharmacology (section 12.3) was updated with relevant PK information; additionally drug metabolizing enzymes and polymorphism information was added.

Metabolism
Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by hydroxylation, yielding both active and inactive metabolites. The major metabolite (11-hydroxy-delta-9-THC) is pharmacologically active. Published *in vitro* data indicates that CYP2C9 and CYP3A4 are the primary enzymes in the metabolism of dronabinol. CYP2C9 appears to be the enzyme responsible for the formation of the principle active metabolite. *[see Pharmacogenomics (12.5)]*.

Pharmacogenomics
Published data indicates a 2 to 3 fold higher dronabinol exposure in individuals carrying genetic variants associated with diminished CYP2C9 function.

Drug Interactions (section 7.0) was updated with literature-derived information:

[redacted]

Effect of other drugs on dronabinol PK: Dronabinol is primarily metabolized by CYP2C9 and CYP3A4 enzymes. Inhibitors of these enzymes may increase, while inducers may decrease, the systemic exposure of the drug and/or active metabolite. [redacted] or loss of efficacy of SYNDROS. Monitor [redacted] for increased adverse reactions [redacted] inhibitors of CYP2C9 [e.g. Amiodarone, fluconazole [redacted] and inhibitors of CYP3A4 enzymes [e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, erythromycin, grapefruit juice [redacted].

4 Appendices

4.1 Individual Study Reviews

Protocol INS-12-015
A Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 4.25 mg versus Marinol® Capsules 5 mg under Fasted Conditions

Design and treatments: This was a pivotal, single dose, open-label, randomized, four-period, two -treatment, two-sequence (TRTR, or RTRT), replicate design, crossover study in 52 healthy male and female adult volunteers (18-53 years of age). Subjects received each treatment twice [i.e. replicates of test (dronabinol oral solution; 4.25 mg in 0.85 mL; Lot: 100310; Insys therapeutics) or reference (Marinol capsules; 5 mg; Lot: 277967A; Banner Pharmacaps for Abbott)] in the four study periods and were randomly assigned to one of the two sequences (TRTR or RTRT). There was a washout of 7 days between the periods. Dosing was done at a pre-specified time each morning, under fasted conditions (at least 10 h of overnight fast and 4 h fasting after the dose).

Blood samples for pharmacokinetic analysis were obtained within each period, at pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose. Plasma was obtained and stored at -20°C or lower for transfer to (b) (4) for sample analyses. Human plasma samples were analyzed for delta9-THC (primary analyte for formulation comparison) and 11-OH-delta9-THC (active metabolite, supportive data) according to (b) (4) procedure ATM-1683, Revision 3. The assay validation is reported under (b) (4) DCN 11-691-V2. The method used in this study was validated for a range of 0.0250 to 10.0 ng/mL based on the analysis of 0.5 mL of plasma.

Disposition: 50 subjects completed all four periods, 1 withdrew prior to the completion of the first two periods, and one completed 2 of the 4 periods.

PK and statistical Results:

Dronabinol (delta9-THC):

Descriptive Statistics of PK data for Dronabinol (reviewer NCA analyses):

A.Mean ± SD Tmax: Median [Range] N = 50-51	Test (Insys) Delta9-THC Replicate 1	Test (Insys) Delta9-THC Replicate 2	Ref (Marinol) Delta9-THC Replicate 1	Ref (Marinol) Delta9-THC Replicate 2
Cmax (ng/mL)	1.81 ± 1.25	2.08 ± 1.34	2.2 ± 1.5	2.6 ± 1.68

Tmax (h)	1.5 [0.5 – 4.0]	1.0 [0.5 – 3.0]	1 [0.5 – 4.0]	1.5 [0.5 – 6.0]
AUClast(ng.h/mL)	3.44 ± 1.98	3.61 ± 1.75	3.75 ± 2.35	4.22 ± 2.65
AUCinf (ng.h/mL)	3.71 ± 2.02	3.88 ± 1.81	3.86 ± 2.4	4.37 ± 3.72
T1/2 (h)	5.22 ± 2.8	5.8 ± 3.0	2.35 ± 2.17	3.16 ± 2.85

Descriptive Statistics of PK data for 11-hydroxy Dronabinol (reviewer NCA analyses):

A.Mean ± SD Tmax: Median [Range] N = 50-51	Test (Insys) 11-OH-Delta9-THC Replicate 1	Test (Insys) 11-OH-Delta9-THC Replicate 2	Ref (Marinol) 11-OH-Delta9-THC Replicate 1	Ref (Marinol) 11-OH-Delta9-THC Replicate 2
Cmax (ng/mL)	2.53 ± 1.38	3.01 ± 1.56	3.28 ± 1.77	3.98 ± 2.50
Tmax (h)	1.5 [0.75 – 4.0]	1.5 [0.5 – 3.0]	1.6 [0.75 – 6.0]	1.5 [0.5 – 6.0]
AUClast(ng.h/mL)	10.05 ± 5.2	11.07 ± 5.05	12.25 ± 6.2	13.44 ± 7.1
AUCinf (ng.h/mL)	10.68 ± 5.43	11.72 ± 5.2	12.9 ± 6.5	14.1 ± 7.3
T1/2 (h)	11.36 ± 4.77	11.96 ± 4.25	11.5 ± 4.4	11.9 ± 3.8

Statistical analyses:
Parent drug (delta9-THC): As the within subject PK variability (s_{WR}) exceeded 0.294 for Marinol (reference) with regard to all three PK parameters, the code automatically adopted the reference-scaled BE approach in assessing bioequivalence:

Parameter	T/R Ratio	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.95	0.1886051	0.4342869	-0.103484	Scaled/PE	PASS
LAUCI	0.93	0.2107749	0.4591023	-0.102459	Scaled/PE	PASS
LCMAX	0.83	0.4232008	0.6505388	-0.176975	Scaled/PE	PASS

The two criteria were met i.e. test to reference geometric mean ratio (GMR) was within 0.8-1.25 and the criteria bound was less than zero. Hence the analysis supports bioequivalence of the test and reference dronabinol products with respect to parent dronabinol, under fasted conditions.

The sponsor in their analysis of dronabinol data, utilized reference-scaled BE approach for Cmax, and average BE approach for AUCT and AUCinf. The within-subject variability of the test product was considered in selecting the type of analysis. While the guidance allows mixed approach based on the variability of each PK parameter, this decision should be based on the variability of the PK parameters for the reference product, and not the test. Nevertheless, it appears that using this mixed approach sponsor was able to demonstrate bioequivalence of the two formulations for all PK parameters.

Using a standard (average) bioequivalence approach (analysis conducted in Pharsight Phoenix after averaging the replicates for test and reference formulations), reviewer was able to generate the following statistical output:

	AUCT	AUCINF	CMAX
Test/Ref GMR [90 % CI]	91.60 [81.98 – 102.36]	99.51 [88.23 – 112.23]	82.33 [74.69 – 90.75]

Using the average BE approach, for dronabinol, the AUC parameters pass the average bioequivalence criteria, while the lowest 90 % CI bound of the Test to reference GMR parameter for Cmax falls below the 80 % threshold.

Metabolite (11-hydroxy delta9-THC):

BE analysis was conducted for the active metabolite 11-hydroxy delta9-THC, as supportive information. As the within-subject PK variability (sWR) for this analyte following the reference Marinol formulation was < 0.294 for all three parameters, scaled BE is not appropriate and therefore average bioequivalence was employed by the sponsor. The lack of high variability in metabolite PK (i.e. sWR < 0.294) was verified by reviewer analysis as well using SAS 9.3:

	Least Squares Geometric Means		Geometric Mean Ratio (%)*				Within-Subject Standard Deviation†	
	Insys	Marinol					Insys	Marinol
Parameter	Lot No. 100310	Lot No. 277967A	Estimate	90% Confidence Interval			Lot No. 100310	Lot No. 277967A
Insys Lot No. 100310 vs. Marinol Lot No. 277967A								
Cmax	2.36	3.05	77.33	72.50	→	82.49	0.287	0.265
AUC(0-t)	9.05	10.90	82.97	77.98	→	88.28	0.214	0.218
AUC(inf)	9.67	11.53	83.92	79.02	→	89.11	0.194	0.218

For the active metabolite, the PK parameters failed average bioequivalence criteria modestly, with the lower 90 % confidence bounds falling somewhat below the regulatory threshold of 80 %. The 90 % confidence bounds also did not include 100 %, suggesting exposure from the test formulation on the lower side relative to the reference formulation, for the active metabolite.

Additional information:

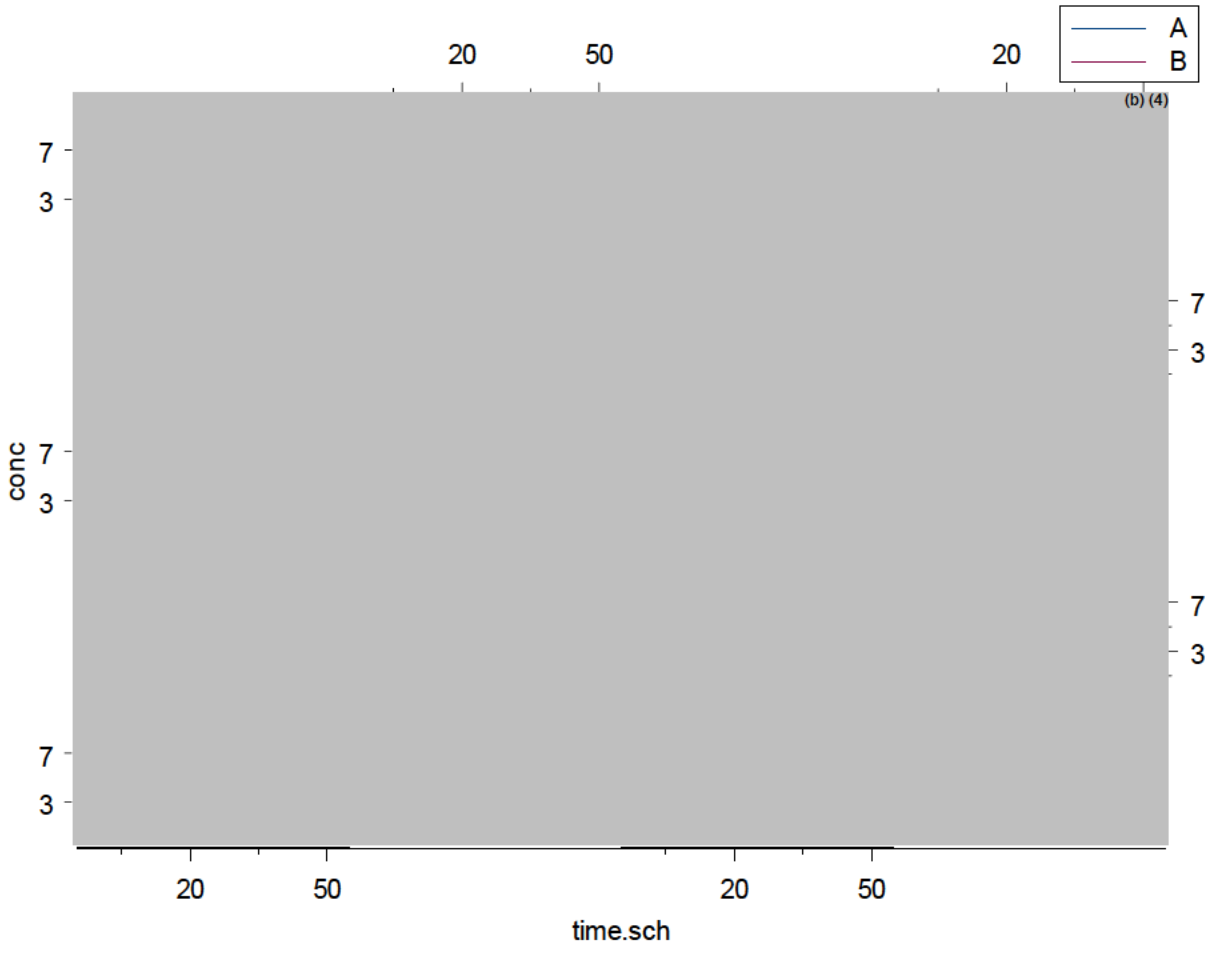
Statistical comparison of the two formulations using average bioequivalence approach is shown below as presented by the sponsor:

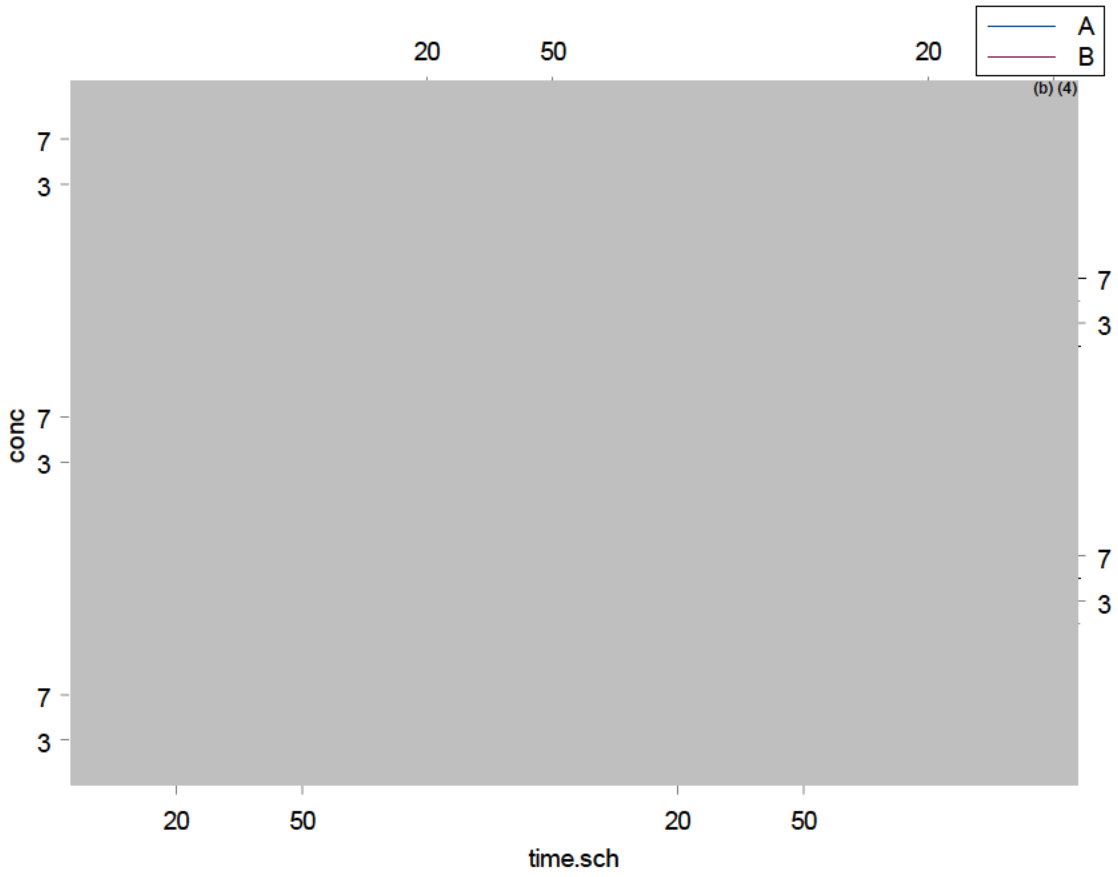
Statistical Analysis of Pharmacokinetic Parameters
Average Bioequivalence

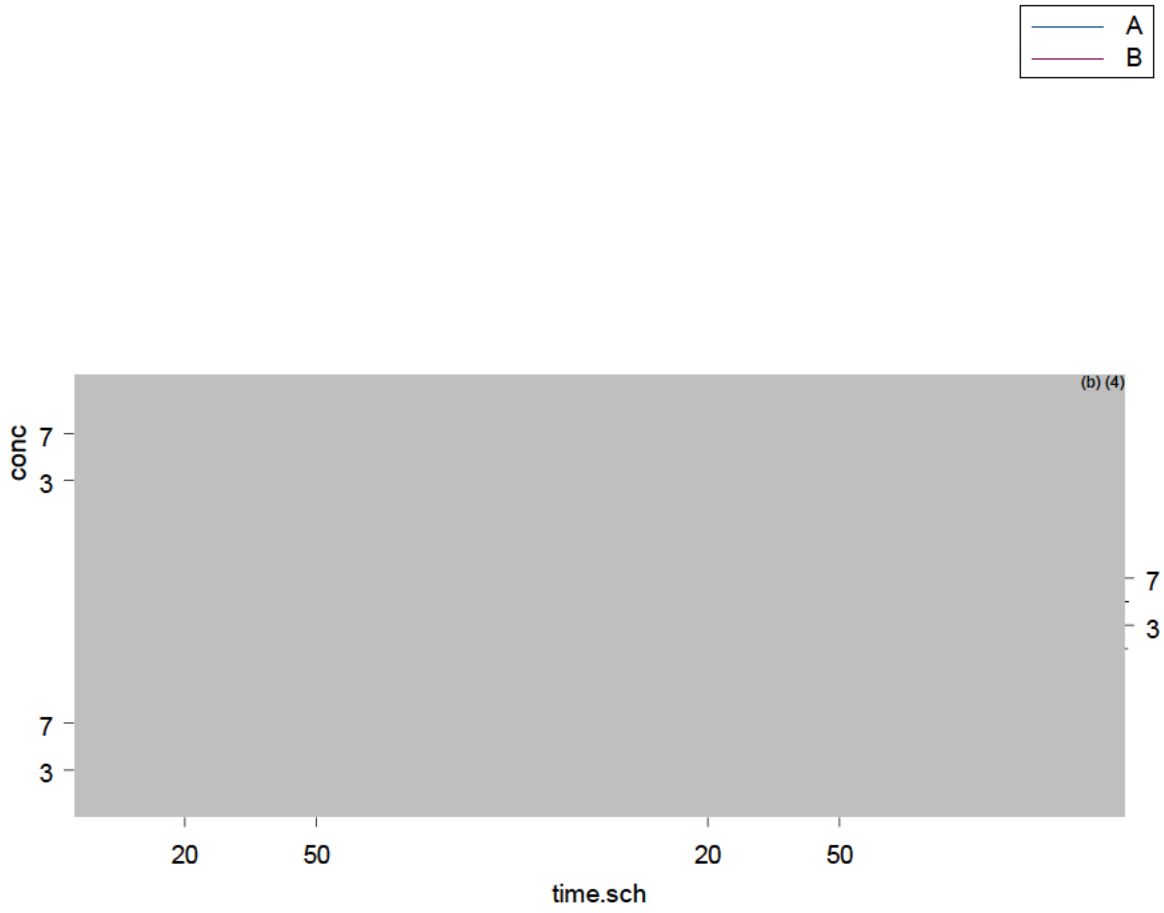
Assay	Parameter	Geometric Means* Test	Geometric Means* Reference	Geometric Mean Ratio	90% Confidence Interval Lower Limit	90% Confidence Interval Upper Limit
Dronabinol	Cmax	1.62	1.97	82.50	74.62	91.22
	AUC(inf)	3.45	3.43	100.39	89.47	112.65
	AUC(0-t)	3.12	3.32	94.07	84.59	104.61
11-OH-Delta 9-THC	Cmax	2.36	3.05	77.33	72.50	82.49
	AUC(inf)	9.67	11.53	83.92	79.02	89.11
	AUC(0-t)	9.05	10.90	82.97	77.98	88.28

Bioanalytical study report: Determination of Delta9-THC and 11-OH-Delta9-THC in Human K2-EDTA Plasma by LC-MS-MS - Insys Therapeutics, Inc. Protocol INS-12-015

The performance of in-study assay standards and QCs, sample stability within storage, and incurred sample reproducibility results support data acceptability for further analyses. Individual profiles of Test (A) and Reference (B)- Includes replicates for each Treatment:







INS004-15-059

An Open-Label, Randomized, Single-Dose, Six-Sequence, Three-Period, Crossover Comparative Bioavailability Study of Dronabinol Oral Solution, 4.25 mg under Fed Conditions, and Marinol Capsule, 5 mg under Fed and Fasted Conditions in Healthy Volunteers

The primary objective of this study was to evaluate the comparative bioavailability of a test product of dronabinol oral solution, 4.25 mg administered under fed conditions to the RLD Marinol (dronabinol) Capsule, 5 mg, when administered to subjects under fed and fasted conditions.

Design: An open-label, randomized, 6-sequence, single dose, 3-period crossover study in 54 healthy male and female volunteers, 18-50 years of age inclusive.
Subjects received each of the following treatments in a randomized sequence:
• Treatment A: Dronabinol oral solution, 4.25 mg, administered under fed conditions
• Treatment B: Marinol (dronabinol) Capsule, 5 mg, administered under fed conditions
• Treatment C: Marinol (dronabinol) Capsule, 5 mg, administered under fasted conditions

Each dose of dronabinol oral solution or Marinol was administered orally with 240 mL of room temperature water. Each drug administration was separated by a washout period of 7 days.

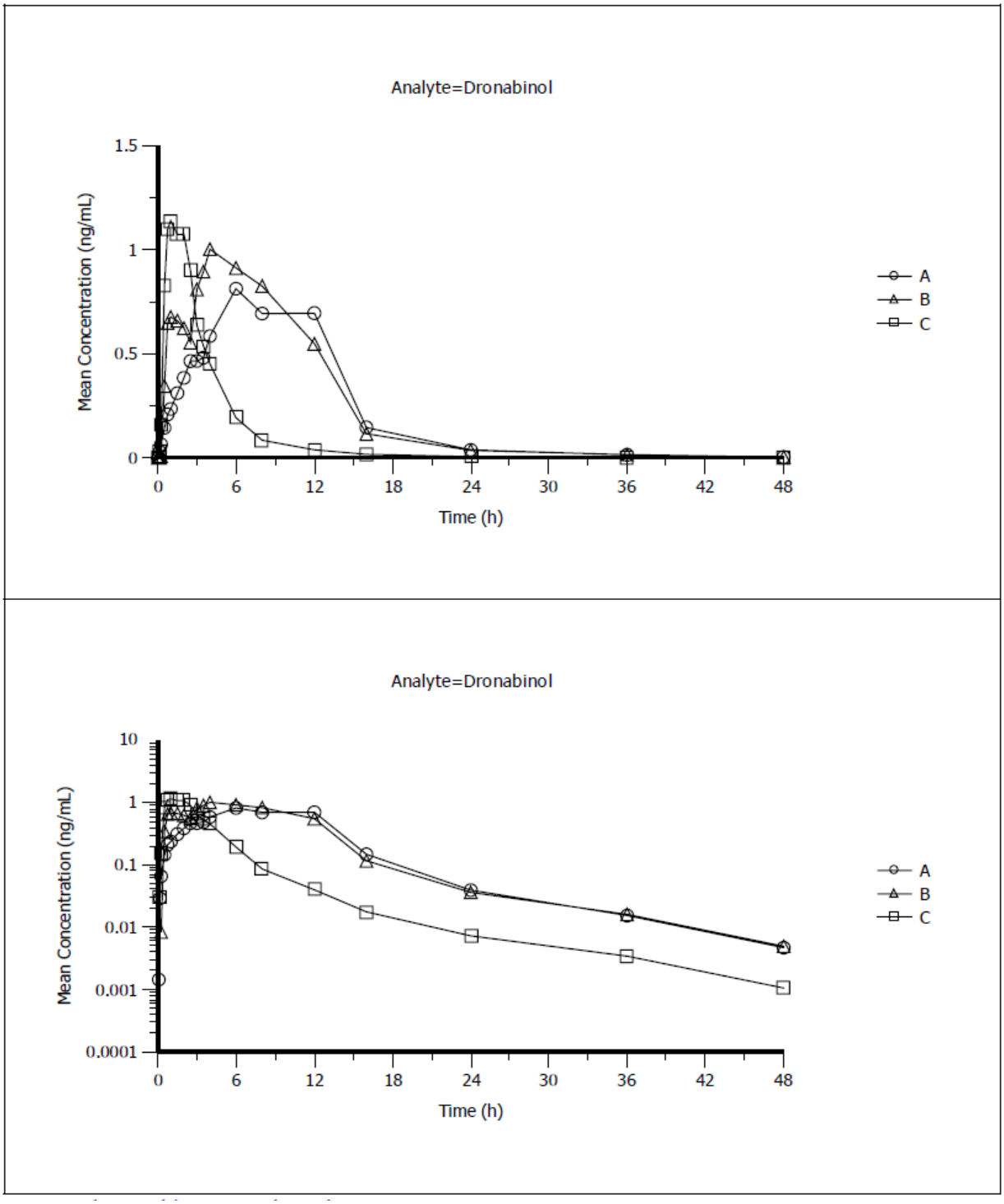
During treatments A and B, subjects received the high-fat, high-calorie breakfast beginning 30 minutes prior to scheduled administration of the dose and ending within 5 minutes prior to dosing. Treatment C was administered to subjects following an overnight fast of at least 10 hours. In each study period, subjects continued to fast for at least 4 hours after study treatment administration.

PK sampling: Blood samples (1 x 6 mL) for dronabinol and its metabolite (11-OH-delta-9-THC) analysis were collected in Vacutainer tubes containing K2-EDTA as a preservative at 0 hour (predose), 0.08 (5 min), 0.17 (10 min), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 16, 24, 36, and 48 hours postdose (20 time points) in each study period.

Sample and data analyses: Plasma samples were analyzed for parent drug and active metabolite using validated analytical methods. Concentration-time data for dronabinol and 11-OH-delta-9-THC were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Statistical analysis was performed using appropriate software, including SAS® (Version 9.3, SAS Institute Inc.), in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation), and Microsoft® Excel® 2013.

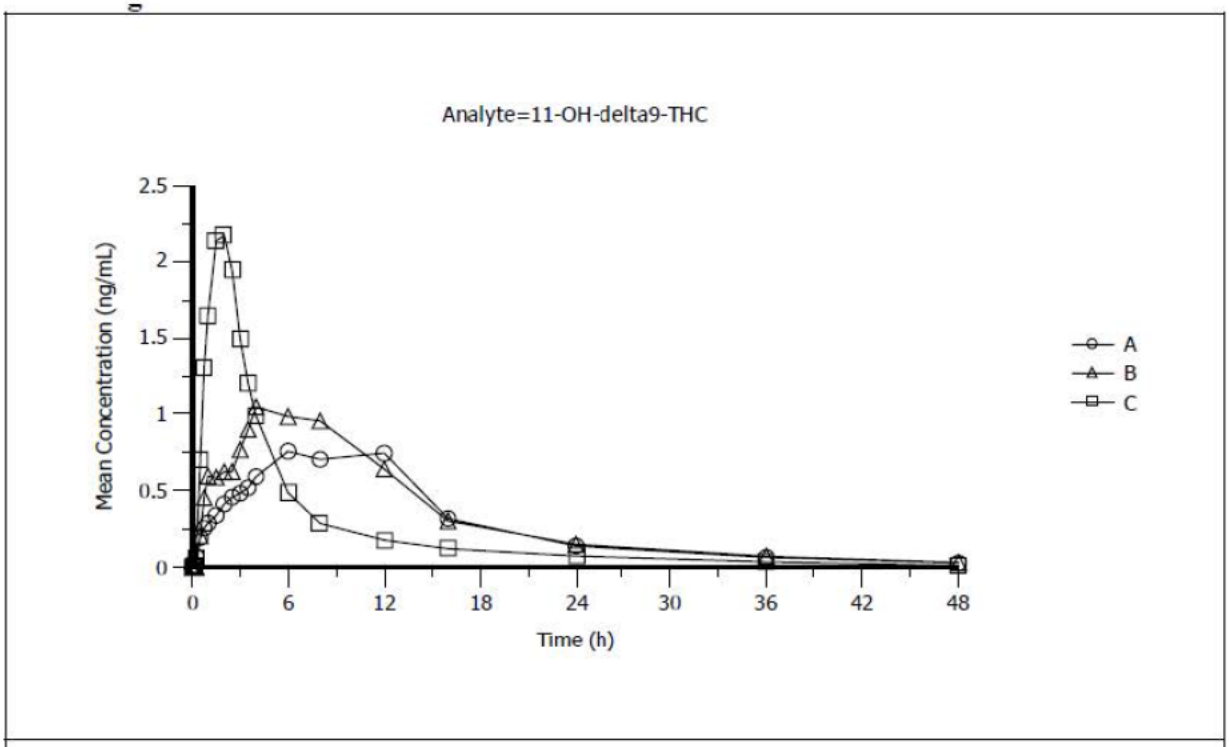
Results and discussion: Subject disposition: Fifty-four (54) subjects were enrolled in the study. There were 27 females and 27 males. Subjects' ages ranged from 23 to 49 years of age. 52 subjects completed all three study periods. Subjects who completed at least one period of the study were included in the pharmacokinetic and statistical analyses.

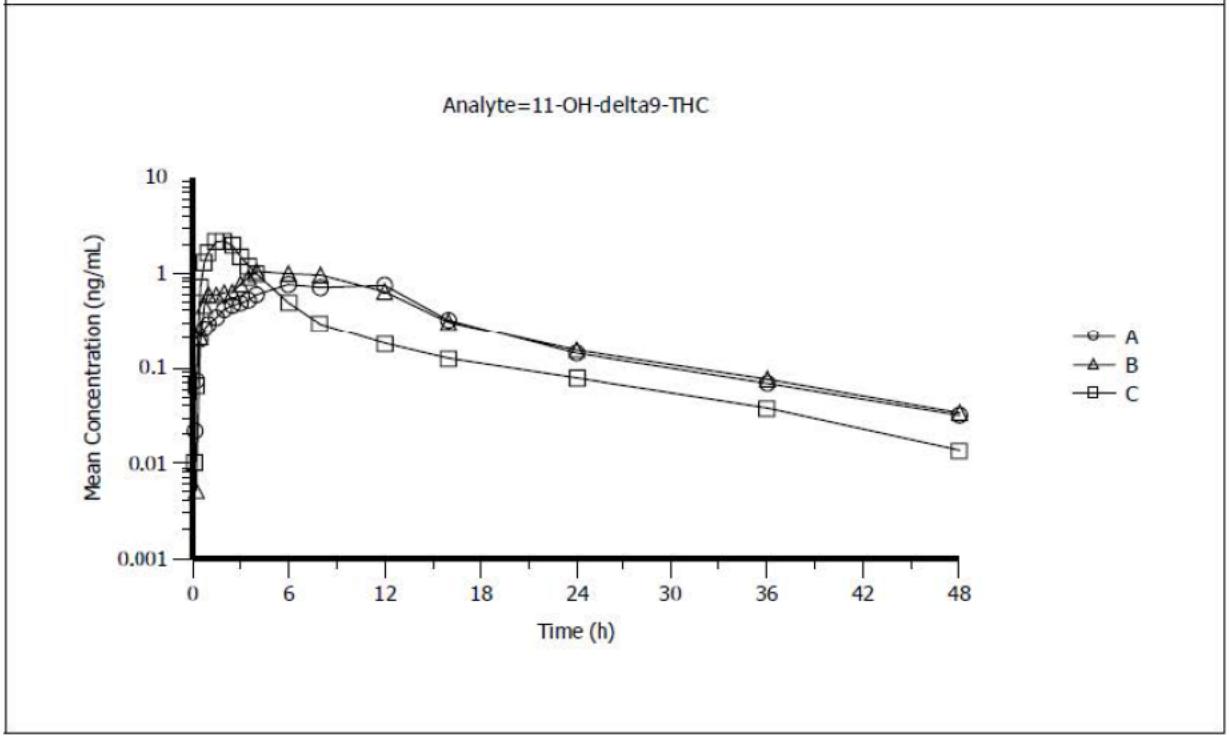
Mean dronabinol concentration-time profiles after Dronabinol Oral Solution, 4.25 mg under fed conditions (Treatment A) and Marinol Capsule, 5 mg under fed (Treatment B) and fasted conditions (Treatment C) on linear and semi-logarithmic scales

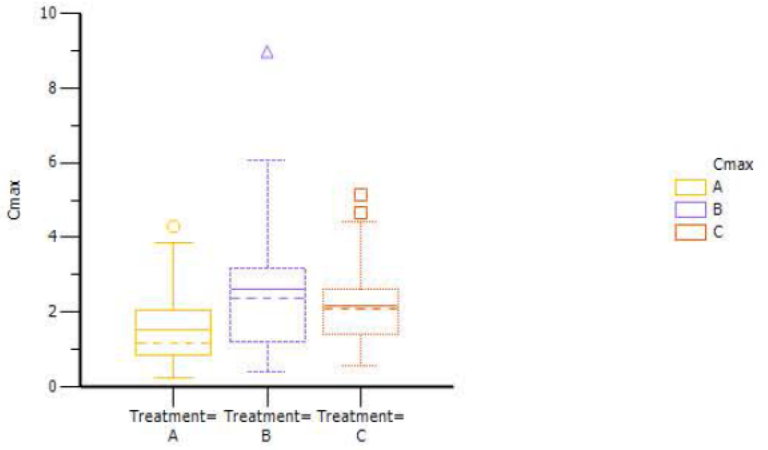


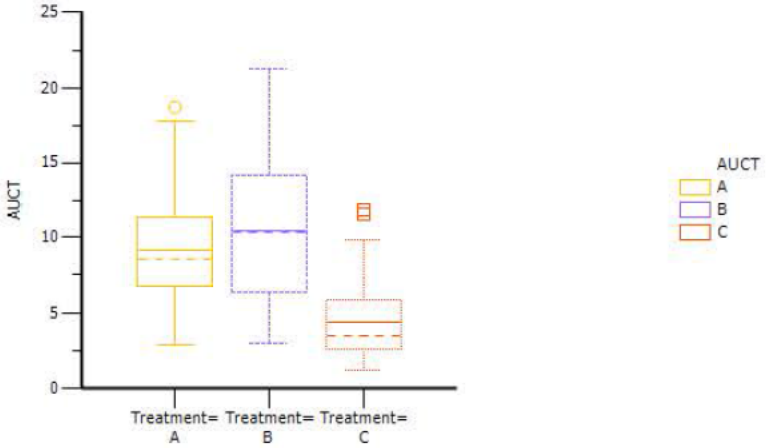
Mean 11-OH-delta-9-THC concentration-time profiles after Dronabinol Oral Solution, 4.25 mg under fed conditions (Treatment A) and Marinol Capsule, 5 mg under fed (Treatment B) and fasted conditions (Treatment C) on linear and semi-logarithmic scales

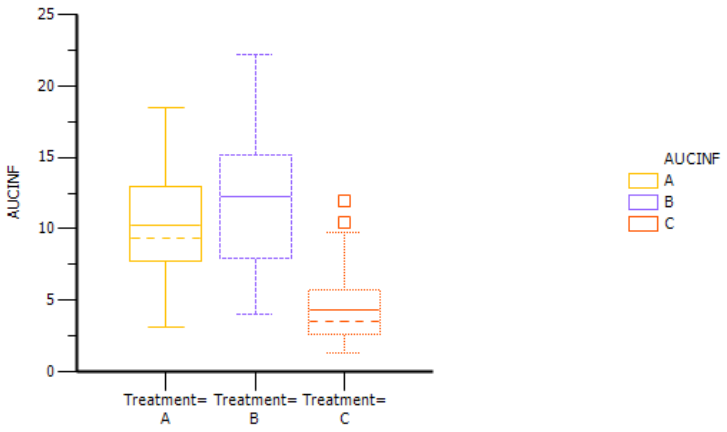
Dronabinol (parent drug) Box plots for exposure parameters:


Analyte=11-OH-delta9-THC
Mean Concentration (ng/mL)
2.5
2
1.5
1
0.5
0
0
6
12
18
24
30
36
42
48
Time (h)
A
B
C


Analyte=11-OH-delta9-THC
Mean Concentration (ng/mL)
10
1
0.1
0.01
0.001
0
6
12
18
24
30
36
42
48
Time (h)
A
B
C

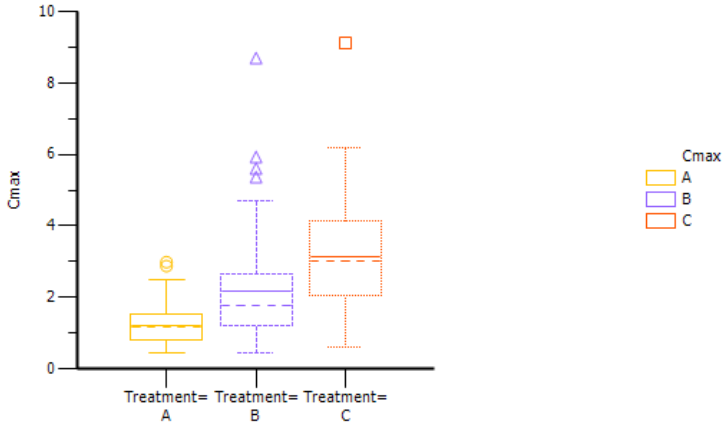

Cmax
10
8
6
4
2
0
Treatment= A
Treatment= B
Treatment= C
Cmax
A
B
C

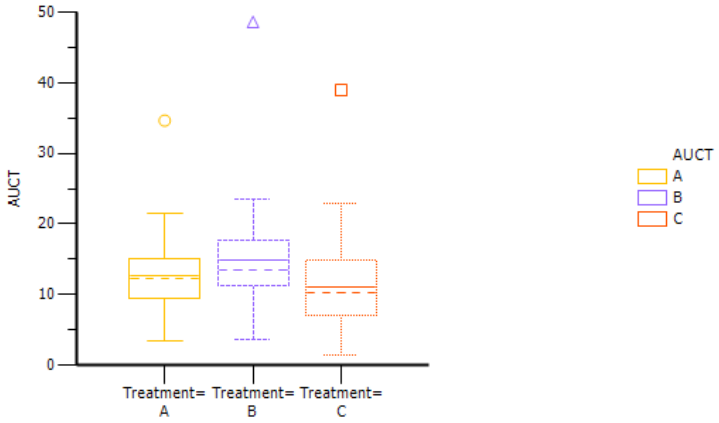

AUCT
25
20
15
10
5
0
Treatment= A
Treatment= B
Treatment= C
AUCT
A
B
C

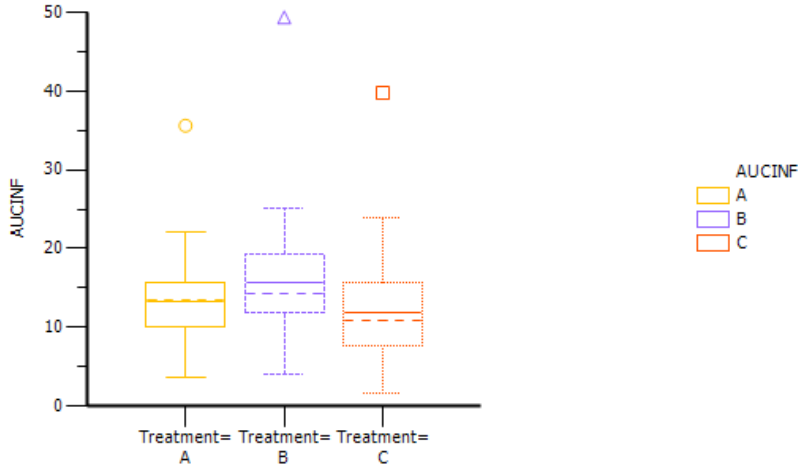


(A = Dronabinol solution fed; B = Marinol capsule fed; C = Marinol capsule fasted)

Active metabolite box plots for systemic exposure parameters:







(A = Dronabinol solution fed; B = Marinol capsule fed; C = Marinol capsule fasted)

Dronabinol PK Descriptive Statistics from the fed BA study:

	Test solution (fed)	Marinol (fed)	Marinol (fasted)
Cmax (ng/mL)	1.52 ± 0.97 (63.52 %)	2.60 ± 1.74 (67.11 %)	2.19 ± 1.06 (48.51 %)
AUC0-t (ng.h/mL)	9.10 ± 3.84 (42.20 %)	10.47 ± 4.85 (46.29 %)	4.44 ± 2.67 (60.17 %)
AUCinf (ng.h/mL)	10.25 ± 3.78 (36.87 %)	12.21 ± 4.83 (39.61 %)	4.33 ± 2.49 (57.52 %)

Reviewer comments:

- A marked food-effect on PK is noted for the Marinol 5 mg formulation.
- A cross study comparison on the dronabinol test solution when dosed under fasted conditions (study INS-12-015) suggests that there is a significant effect of food on the dronabinol PK from the test solution, similar to that seen with Marinol.
- The Cmax for the test formulation (dronabinol oral solution) under fed conditions is lower compared to Marinol under fed or fasted conditions.
- The AUCs of dronabinol from the test solution under fed conditions fell within the range noted for Marinol under fasted and fed conditions.

Metabolite PK Descriptive Statistics from the fed BA study:

	Test solution (fed)	Marinol (fed)	Marinol (fasted)
Cmax (ng/mL)	1.23 ± 0.60 (49.14 %)	2.16 ± 1.50 (69.58 %)	3.12 ± 1.67 (53.42 %)
AUC0-t (ng.h/mL)	12.61 ± 5.10 (40.44 %)	14.84 ± 6.49 (43.70 %)	11.17 ± 6.07 (54.34 %)
AUCinf (ng.h/mL)	13.29 ± 5.23 (39.39 %)	15.59 ± 6.67 (42.77 %)	11.81 ± 6.18 (52.27 %)

Reviewer comments:

- Reference Marinol PK under fed and fasted conditions suggests a modest increase in AUC parameters of the active metabolite under fed conditions.
- A cross study comparison of the metabolite PK from the dronabinol test solution when dosed under fasted conditions (study INS-12-015) does not suggest a significant food-effect on PK of active metabolite, similar to that seen with Marinol.
- The metabolite Cmax from the test formulation (dronabinol oral solution) under fed conditions is lower compared to metabolite Cmax from Marinol under fed or fasted conditions.
- The AUCs of active metabolite from the test solution under fed conditions fell within those noted for Marinol under fasted and fed conditions.

Relative Bioavailability summary for parent dronabinol:

Solution-fed (test) vs. Marinol fed (reference):

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	60.80	51.99	71.10
AUCT	88.93	79.08	100.00
AUCINF	81.93	69.04	97.24
Test: Solution-fed; Reference: Marinol-fed			

Reviewer comments:

- This was the primary comparison of interest in this study. Relative BA statistics suggest that AUCt values were comparable for the test (solution) and reference (capsule) formulations under fed conditions. The lower 90 % confidence bound for AUCinf was below the 80 % regulatory threshold for bioequivalence. The Cmax for the oral solution was lower compared to Marinol under fed conditions.

Solution-fed (test) vs. Marinol fasted (reference):

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	64.89	55.46	75.93
AUCT	219.14	194.82	246.50
AUCINF	236.61	201.95	277.22
Test: Solution-fed; Reference: Marinol-fasted			

Reviewer comments:

- This comparison of test solution under fed conditions to Marinol under fasted conditions, again showed lower Cmax values for dronabinol under fed dosing. AUCT and AUCinf values suggest a much higher exposure of dronabinol from the test formulation under fed conditions compared reference capsule dosed under fasted conditions. This is consistent with the marked food-effect noted for Marinol capsule as seen in the table below.

Marinol fasted vs. fed:

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	106.73	91.36	124.69
AUCT	246.43	219.31	276.90
AUCINF	288.78	248.18	336.03
Test: Marinol-fed; Reference: Marinol-fasted			

Reviewer comments:

- A significant food-effect on dronabinol PK from Marinol capsule, with an increase in AUCt by ~ 2.5-fold and AUCinf by 2.8-fold is seen. Food did not

increase dronabinol Cmax from Marinol as the point estimate was close to 100 % and the 90 % confidence bounds were within the 80-125 % BE bounds.

Relative Bioavailability summary for the active metabolite:

Metabolite PK: Dronabinol solution (test) vs. Marinol capsule (reference) under fed conditions:

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	61.75	54.96	69.39
AUCT	85.69	80.24	91.51
AUCINF	86.16	80.96	91.70
Test: Solution-fed; Reference: Marinol-fed			

Reviewer comments: Despite a lower Cmax, the metabolite AUCs were comparable to Marinol under fed dosing.

Metabolite PK: Dronabinol solution (fed) vs. Marinol capsule (fasted)

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	41.62	37.03	46.77
AUCT	121.08	113.37	129.32
AUCINF	119.79	112.55	127.50
Test: Solution-fed; Reference: Marinol-fasted			

Reviewer comments: Despite a lower Cmax, the AUCs for the active metabolite were modestly higher for the test formulation under fed dosing to reference under fasted dosing (~ 20 % higher AUCs).

Metabolite PK: Reference Marinol capsule fed vs. fasted:

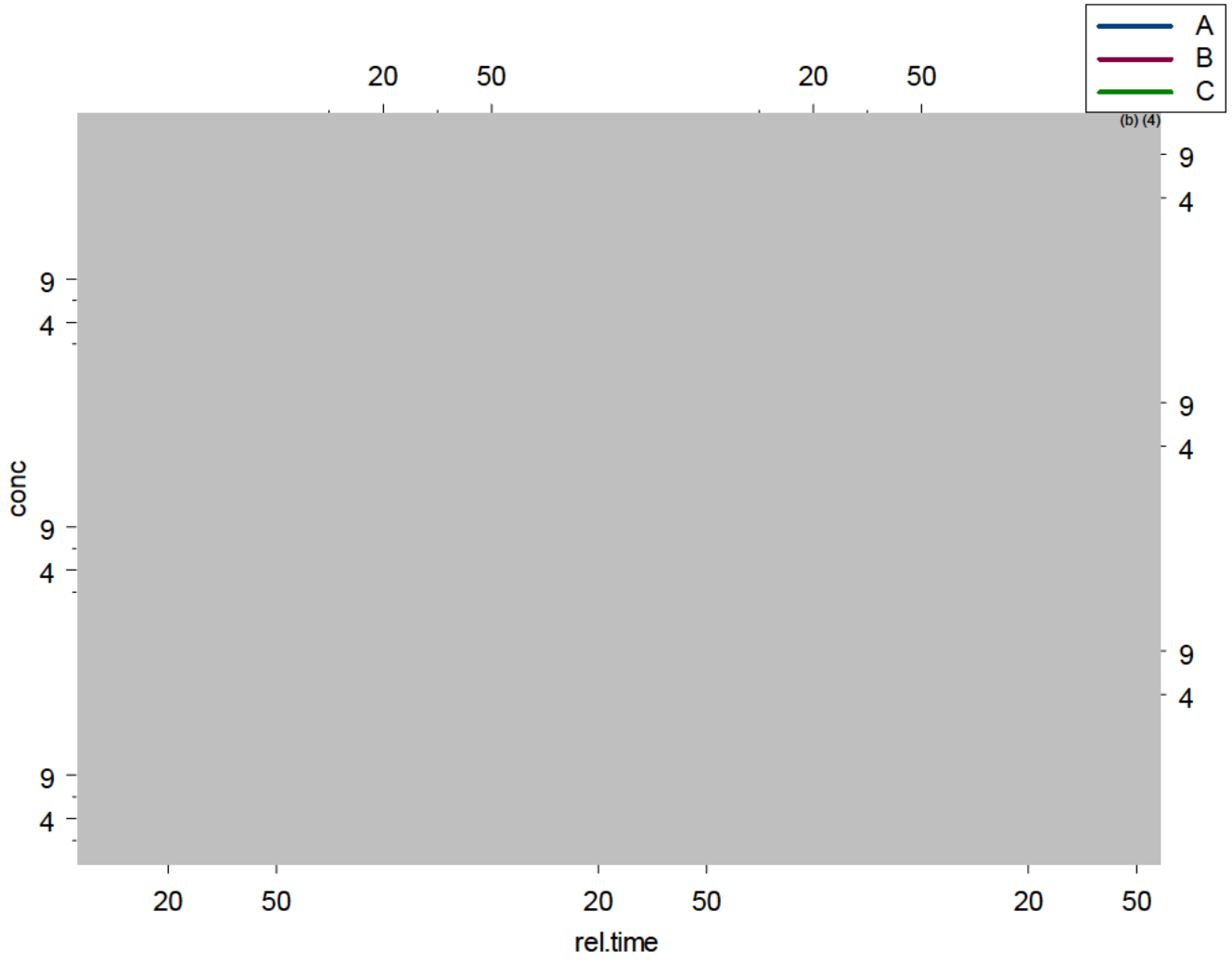
Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	67.39	60.03	75.67
AUCT	141.31	132.38	150.83
AUCINF	139.03	130.69	147.90
Test: Marinol-fed; Reference: Marinol-fasted			

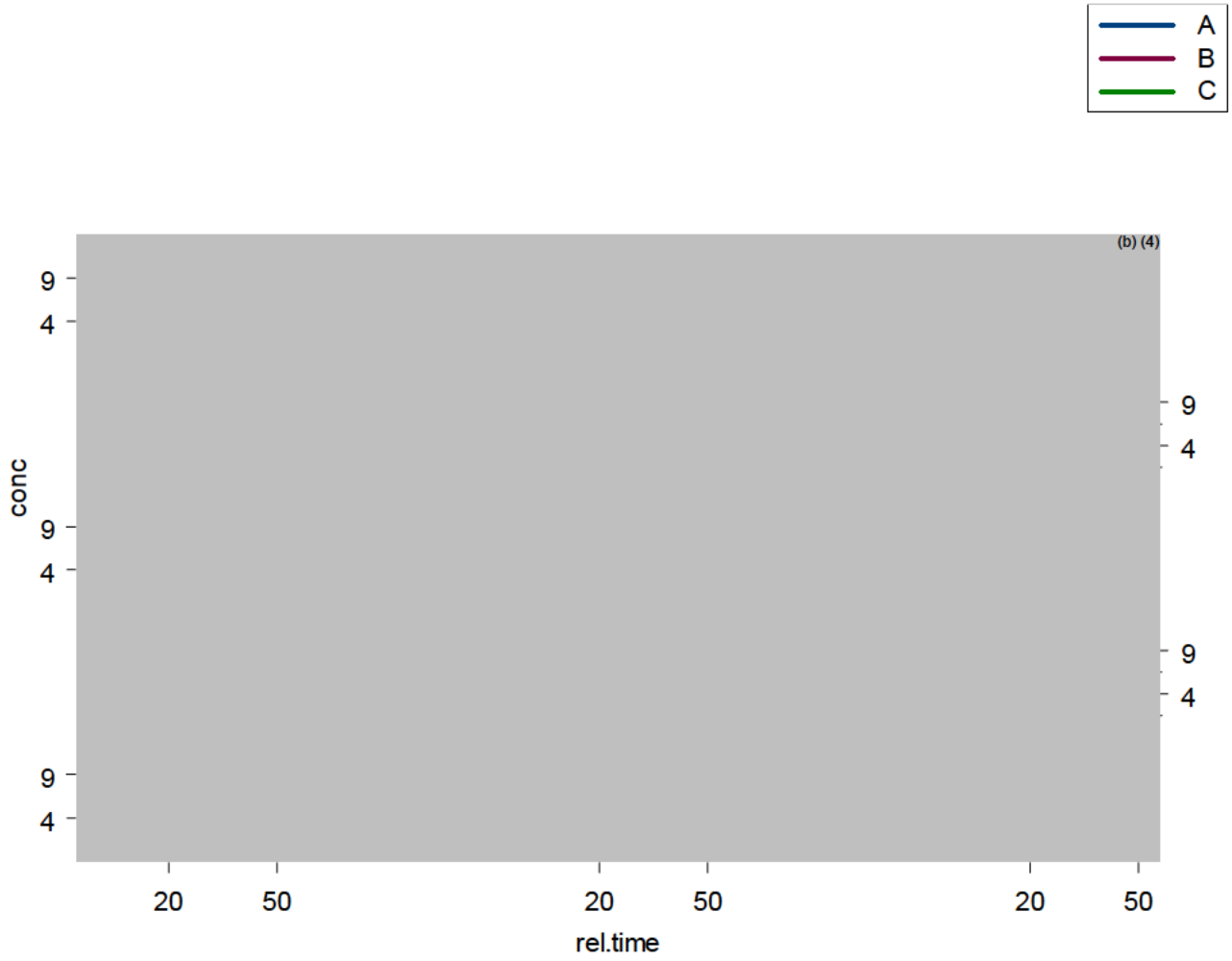
Reviewer comments:

- Despite a lower Cmax, under fed conditions, Marinol capsule showed a modest food-effect on metabolite PK, with increased AUC parameters by ~ 40 %.

Individual profiles of dronabinol:

(A = Dronabinol solution fed; B = Marinol capsule fed; C = Marinol capsule fasted)





(A = Dronabinol solution fed; B = Marinol capsule fed; C = Marinol capsule fasted)

Bioanalytical method validation:

Determination of Δ9-THC (Dronabinol) and 11-OH-Δ9-THC in EDTA Human Plasma by LC-MS-MS

Method: Human plasma containing Δ9-THC, 11-OH-Δ9-THC, and the respective trideuterated internal standards, Δ9-THC-D3 (THC-D3) and 11-OH-Δ9-THC-D3 (11-OH-THC-D3), was mixed with a phosphate buffer and extracted with an ethyl acetate/MTBE mixture. After the analytes were derivatized with nicotinoyl chloride and evaporated, they were dissolved in mobile phase. A portion of the extract was injected onto a SCIEX API 4000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 420→313 THC product ion was measured against the peak area of the m/z 423→316 THC-D3 internal standard product ion. The peak area of the m/z 541→418 11-OH-THC product ion was measured against the peak area of the m/z 544→421 11-OH-THC-D3 internal standard product ion. Quantitation was performed using weighted

(1/x2) linear least squares regression analysis generated from fortified plasma calibration standards prepared immediately prior to each run.

Combined calibration standards for both analytes were prepared by spiking plasma with stock solution to yield standards ranging 0.0250, 0.0500, 0.100, 0.250, 0.500, 2.00, 9.00 and 10 ng/mL for both analytes. For validation, calibration standards were assayed in three separate runs.

QC samples were prepared by fortifying plasma with stock solution at the appropriate concentrations. High, medium, and low QC samples were prepared at 8.00, 4.00, and 0.0750 ng/mL for both analytes. Additionally, a very high dilution QC pool was prepared with stock solution at 50.0 ng/mL for both analytes.

The Δ9-THC-D3 and 11-OH-Δ9-THC-D3 internal standard working solution was prepared to yield a concentration of approximately 0.100 µg/mL each. Each sample was fortified with 20.0 µL of this solution.

The assay procedure was found to be linear over the range of 0.025 to 10 ng/mL for both analytes. Acceptable correlation coefficient (R2), precision and accuracy (using back calculated values) were obtained during calibration standard runs:

Analyte	Slope	Intercept	R^2
Δ9-THC (Table 1)	0.226736	0.001042	0.9943
11-OH-Δ9-THC (Table 2)	0.264424	0.000924	0.9946

Analyte	CV		Bias	
	From	To	From	To
Δ9-THC (Table 1)	1.4%	10.9%	-5.2%	6.4%
11-OH-Δ9-THC (Table 2)	0.2%	11.0%	-6.0%	6.0%

Acceptable precision and accuracy (intra- and inter-run) data were obtained for the QC samples (high, medium, low) are shown below:

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
Δ9-THC (Table 3)	0.7%	5.0%	-7.8%	2.8%	3.4%	4.2%	-3.9%	-0.3%
11-OH-Δ9-THC (Table 5)	0.8%	9.3%	-5.4%	6.1%	1.6%	8.1%	-4.5%	1.3%

Six replicates of the high dilution QC sample (50 ng/mL) suggested acceptable precision and accuracy as shown below, suggesting acceptability of 10-fold dilution:

Intrarun		
Analyte	CV	Bias
Δ9-THC (Table 3)	3.0%	0.0%
11-OH-Δ9-THC (Table 5)	2.5%	9.0%

Bench top stability of the analytes in thawed QC samples was established for 24 hours prior to extraction. Freeze/thaw stability of triplicate QC samples was demonstrated through five cycles. Extract stability was established after reinjecting extracts left at room temperature for ~ 49 hours. Run injection stability was demonstrated.

Recovery was calculated by comparing peak areas of extracted standards to the unextracted standards at three concentrations spanning the calibration curve.

Analyte	Recovery		Internal Standard	Recovery
	From	To		
Δ9-THC (Table 12)	106.9%	119.5%	Δ9-THC-D_3 (Table 12)	117.5%
11-OH-Δ9-THC (Table 13)	96.9%	103.9%	11-OH-Δ9-THC-D_3 (Table 13)	109.1%

Specificity was demonstrated by the absence of interfering peaks in blank plasma at the retention times of drug and metabolite or the internal standards.

Extended stability was evaluated by fortifying plasma pools with the analytes and storing at -20°C. Comparison to a fresh standard curve, suggested acceptable stability for 30 days testing period.
Additional long term stability at -20°C provided in an amendment to the validation report notes that Δ9-THC is stable for 197 days and 11-OH-THC is stable for 355 days under these test conditions.

Method validation summary:

Bioanalytical Method Validation Summary for Δ9-THC in Human K_2-EDTA Plasma

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Δ9-THC
Internal standard (IS)	Δ9-THC-D_3
Method description	ATM-1683; Liquid-liquid extraction; Sciex API 4000 LC-MS-MS; Masterfile 11-691-V2
Limit of quantitation[a]	0.0250, ng/mL
Average recovery of drug (%)[a]	111.8
Average recovery of IS (%)[a]	117.5
Standard curve concentrations (ng/mL)	0.0250 to 10.0 ng/mL
QC concentrations (ng/mL)	0.0750, 4.00, 8.00
QC Intraday precision range (%)	2.1 to 3.0
QC Intraday accuracy range (%)	-9.0 to 12.0
QC Interday precision range (%)[b]	2.7 to 4.3
QC Interday accuracy range (%)[b]	-6.4 to 0.0
Bench-top stability (hrs)[e]	24 hours @ room temperature
Stock stability (days)	93 days @ 4 °C and 45 hours @ room temperature
Processed stability (hrs)	49 hours @ room temperature[a]; 96 hours @ room temperature[e]
Freeze-thaw stability (cycles)[ce]	9 cycles
Long-term storage stability (days)	246 days @ -20 °C[d]; 59 days @ -70 °C[e]
Dilution integrity[a]	50.0 ng/mL diluted 10-fold
Selectivity[a]	No interfering peaks noted in blank plasma samples

[a] Established in human K_3-EDTA plasma, under ATM-798 and reported in 11-691-V2.
[b] Established under ATM-798 and reported in 11-691-V2_am4.
[c] Established under ATM-798 and reported in 11-691-V2_am3.
[d] Established under ATM-798 and reported in 11-691-V2_am5.
[e] Established under ATM-798 and reported in 11-691-V2_am6.

Bioanalytical Method Validation Summary for 11-OH-Δ9-THC in Human K_2-EDTA Plasma

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	11-OH-Δ9-THC
Internal standard (IS)	11-OH-Δ9-THC-D_3
Method description	ATM-1683; Liquid-liquid extraction; Sciex API 4000 LC-MS-MS; Masterfile 11-691-V2
Limit of quantitation[a]	0.0250, ng/mL
Average recovery of drug (%)[a]	100.7
Average recovery of IS (%)[a]	109.1
Standard curve concentrations (ng/mL)	0.0250 to 10.0 ng/mL
QC concentrations (ng/mL)	0.0750, 4.00, 8.00
QC Intraday precision range (%)	2.1 to 3.8
QC Intraday accuracy range (%)	-11.0 to 10.8
QC Interday precision range (%)[b]	1.9 to 6.5
QC Interday accuracy range (%)[b]	-8.0 to 0.1
Bench-top stability (hrs)[e]	24 hours @ room temperature
Stock stability (days)	93 days @ 4 °C and 45 hours @ room temperature
Processed stability (hrs)	49 hours @ room temperature[a]; 96 hours @ room temperature[e]
Freeze-thaw stability (cycles)[ce]	9 cycles
Long-term storage stability (days)	246 days @ -20 °C[d]; 59 days @ -70 °C[e]
Dilution integrity[a]	50.0 ng/mL diluted 10-fold
Selectivity[a]	No interfering peaks noted in blank plasma samples

[a] Established in human K_3-EDTA plasma, under ATM-798 and reported in 11-691-V2.
[b] Established under ATM-798 and reported in 11-691-V2_am4.
[c] Established under ATM-798 and reported in 11-691-V2_am3.
[d] Established under ATM-798 and reported in 11-691-V2_am5.
[e] Established under ATM-798 and reported in 11-691-V2_am6.

Additional extracted sample stability data has been generated for up to 125 days at RT (amendment 8).

The method ATM-798 in K3-EDTA plasma was initially validated under (b) (4) *DCN 11-691-V2 in 2004. Subsequently study amendments through 2012 resulted in the partial validation of revised method ATM-1683 and qualified qualify additional reference standards, sample matrix (K2-EDTA plasma) and provided additional stability data in the original and new matrices.*

Protocol INS-10-012

A single-dose, replicate, crossover design, comparative bioavailability study of dronabinol oral solution 5 mg versus Marinol capsules 5 mg under fasted conditions

Study design: Single dose, open-label, randomized, four-period, two-sequence, replicate design crossover study with a 7-day washout between study periods. 88 healthy subjects (18- 55 years) were enrolled to receive four separate single-dose administrations of dronabinol oral solution (5 mg dose in 1 mL; Lot 100310) or Marinol capsules (5 mg dose; Lot 200994A) in four study periods following an overnight fast of at least 10 hours. Subjects also fasted for 4 hours after dosing. Subjects were randomized to one of the two dosing sequences (TRTR or RTRT). Subjects received each treatment twice in a two-sequence randomized fashion during the four treatment periods.

Disposition: Out of the 88 subjects enrolled, 82 completed all four study periods. The remaining six subjects withdrew from the study due to personal or compliance reasons after completion of one, two or three study periods. Overall, data from 85 subjects was included in the analysis, 82 of whom completed all 4 treatments, 2 that completed 3 of the 4 treatments, and 1 that completed 2 of the 4 treatments.
Blood samples were obtained at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hr post-dose to determine the pharmacokinetic profile and exposure of dronabinol after each treatment. Samples were collected into appropriately labeled, 6 mL Vacutainer tubes containing K2-EDTA and held in an ice water bath immediately after being drawn. Blood samples were centrifuged at approximately 2500 rpm for 15 minutes at approximately 4 °C and the resulting plasma was transferred to an appropriately-labeled polypropylene screw-cap tube. Within 45 minutes of collection, samples were frozen at approximately -20 °C or lower pending transfer to (b) (4) for analysis.

Human plasma samples were analyzed for delta9-THC and 11-OH-delta9-THC according to (b) (4) procedure ATM-1683, Revision 3. The assay validation was finalized and reported under (b) (4) DCN 11-691-V2. The method used in this study was validated for a range of 0.0250 to 10.0 ng/mL for each analyte based on the analysis of 0.500 mL of plasma. Method validation and bioanalytical assay report review supports the use of plasma concentration data generated for dronabinol and its metabolite in the derivation of pharmacokinetic parameters for further statistical analyses.

PK parameters were obtained using non-compartmental analysis of plasma concentration-time data for the parent drug and the active metabolite. Statistical analyses were performed using SAS 9.3 to evaluate bioequivalence.

Study INS-10-012 Results:

Descriptive Statistics for dronabinol ((Delta9-tetrahydrocannabinol; PK parameters generated using Pharsight Phoenix):

Dronabinol Mean ± SD *Median[Range]	Test [Insys dronabinol solution; 5 mg]		Reference [Marinol 5 mg capsule]	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2
Cmax (ng/mL)	2.33 (1.23)	2.50 (1.36)	2.05 (0.95)	2.28 (1.45)
Tmax (h)*	1.0 [0.25 – 4.0]	1.0 [0.25 – 2.5]	1.5 [0.5- 6.0]	1.0 [0.5 – 6.0]
AUCt (ng.h/mL)	4.14 (1.95)	4.31 (2.0)	3.35 (2.16)	3.72 (2.2)
AUCinf (ng.h/mL)	4.45 (2.08)	4.66 (2.19)	3.55 (2.5)	3.96 (2.44)
T1/2 (h)	7.12 (5.6)	8.2 (6.7)	4.0 (9.8)	5.4 (10)

Statistical analyses for dronabinol (SAS 9.3): For the parent drug, the code employed scaled BE analysis, as the intra subject variability factor sWR exceeded 0.294 for all three dronabinol PK parameters.

Parameter	**T/R Ratio**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT	1.26	0.164022	0.4049963	-0.034187	Scaled/PE	FAIL
LAUCI	1.36	0.1565893	0.3957137	0.0325134	Scaled/PE	FAIL
LCMAX	1.12	0.1378274	0.3712511	-0.067927	Scaled/PE	PASS

Only Cmax passed both the BE criteria for reference scaled BE analysis i.e. point estimate (T/R GMR) between 0.8 – 1.25 and the criteria bound of less than zero. AUCT and AUCinf failed the RSABE analyses, as they either failed one or both of the success criteria. Overall, the point estimate suggested higher exposure (AUC) to dronabinol following the Insys oral solution, compared to Marinol 5 mg capsules when administered at identical doses.

Descriptive Statistics for metabolite, 11-hydroxy delta9-tetrahydrocannabinol; PK parameters generated using Pharsight Phoenix:

Metabolite Mean (SD)	Test [Insys dronabinol solution; 5 mg]		Reference [Marinol 5 mg capsule]	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2
Cmax (ng/mL)	3.2 (1.5)	3.5 (1.7)	3.1 (1.5)	3.6 (1.9)

Tmax (h) Median[Range]	1.5 [0.75 – 4.0]	1.5 [0.5 – 3.0]	1.5 [0.75 – 6.0]	1.5 [0.75 – 6.0]
AUCt (ng.h/mL)	11.8 (5.4)	12.9 (5.9)	10.9 (5.4)	12.6 (6.7)
AUCinf (ng.h/mL)	12.5 (5.5)	13.7 (6.0)	11.6 (5.6)	13.4 (7.0)
T1/2 (h)	13.2 (5.1)	13.1 (4.6)	12.2 (4.6)	12.4 (4.4)

Statistical analyses for 11-hydroxy-delta9-THC (SAS 9.3): For the metabolite, the code employed scaled BE analysis only for Cmax, where the intrasubject variability parameter sWR exceeded 0.294. For the remaining two parameters, as sWR was < 0.294, unscaled (average) BE was employed.

Parameter	**T/R Ratio**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**Outcome**
LCMAX	*0.99*	*0.0874009*	*0.2956365*	*-0.055071*	*Scaled/PE*	*PASS*

Average (unscaled) bioequivalence analysis was also conducted (primarily for the two AUC parameters, where intrasubject variability parameter, wSR was < 0.294; see above table) using Pharsight Phoenix. All three metabolite PK parameters were deemed bioequivalent using the standard BE approach:

Metabolite PK	Test/Reference (GMR)	90 % Confidence Interval
AUCT	106.2	102.5 – 109.9
AUCINF	105.8	101.5 – 110.4
CMAX	98.7	94.2 – 103.5

Thus the metabolite passed the bioequivalence criteria for Cmax (using RSABE) and for AUC parameters (using average BE).

Overall, in study INS-10-012, dronabinol oral solution (5 mg in 1 mL) was not bioequivalent to reference Marinol capsule (5 mg). Exposure (AUC) of the parent dronabinol was on average ~ 35 % higher from the solution compared to reference Marinol capsules. Metabolite PK data support bioequivalence across the two formulations.

Study INS-08-008
A Pilot, Pharmacokinetic Profile and Comparative Bioavailability Study of Dronabinol Syrup 10 mg, Dronabinol Oral Solution 10 mg and Marinol® (Dronabinol) Capsules 10 mg under Fasted Conditions

Study design and objectives: Single-dose, three-period, three-sequence crossover study with a seven-day washout between study periods. A total of 18 male and female subjects were enrolled into the study. The primary objective of this trial was to assess the

pharmacokinetic profile and bioavailability of dronabinol from the test formulations relative to reference Marinol, 10 mg.
Treatments: Note that test product (A) termed Dronabinol oral syrup 5 mg/mL is similar to the one used in pivotal bioequivalence trials, while the test product (B) termed Dronabinol oral solution 5 mg/mL is an early formulation that was based on (b) (4) .

Test Product, Dose and Mode of Administration, Lot Number: Dronabinol Oral Syrup 5 mg/mL Dose = 10 mg (2 mL), oral administration Lot: 805588
Test Product, Dose and Mode of Administration, Lot Number: Dronabinol Oral Solution 5 mg/mL Dose = 10 mg (2 mL), oral administration Lot: 805587
Duration of Treatment: Three single dose treatments were administered with a 7-day washout period between doses.
Reference Product, Dose and Mode of Administration, Lot Number: Marinol® 10 mg Dose = 1 x 10 mg capsule, oral administration Lot: 28050513A

Reviewer analysis: The relative bioavailabilities of the two pilot formulation vs, Marinol (10 mg) are summarized below:
Test A: 10 mg Syrup; comparable to dronabinol oral solution used in studies 012 and 015)
Test B (10 mg solution; (b) (4) based formulation; not used in pivotal BE trials)
Reference C (10 mg Marinol Capsule)

	TRT	T/R (%)	90 % CI LB	90 % CI UB
CMAX	A	85.02687	68.30164	105.8477
CMAX	B	40.88631	32.84376	50.89826
AUCT	A	111.3647	95.69451	129.6009
AUCT	B	121.5406	104.4385	141.4431
AUCINF	A	112.3355	96.24205	131.1201
AUCINF	B	121.7347	103.9414	142.5739

Review of literature and other published sources:

The following resources were primarily used in identifying relevant drug metabolism, polymorphism and drug interaction information for dronabinol (also referred to as delta (9)-tetrahydrocannabinol or THC):

1. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes; Watanabe et al, Life Sciences 80 (2007) 1415–1419

2. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review; Stephen M. Stout and Nina M, Cimino, Drug Metab Rev. 2014 Feb; 46(1):86-95.

3. Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity; Yamaori et al, Drug Metab Pharmacokinet. 2012; 27(3):294-300.

4. CYP2C-catalyzed delta (9)-tetrahydrocannabinol metabolism: Kinetics, pharmacogenetics and interaction with phenytoin; Bland et al, Biochemical Pharmacology 70 (2005) 1096–1103.

5. Inter-individual variation in the pharmacokinetics of Delta9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9; Sachse-Seeboth et al, Clin Pharmacol Ther. 2009 Mar; 85(3):273-6.

6. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers; Stott et al, Springerplus 2013 May 24; 2(1):236

The following conclusions could be drawn from these publications:

- CYP2C9 and CYP3A4 enzymes are primarily involved in the metabolism of dronabinol. In this study, delta9-tetrahydrocannabinols (dronabinol) was mainly oxidized at the 11-position and at the 8β-position in human hepatic microsomes. The 11-hydroxylation by the microsomes was markedly inhibited by sulfaphenazole, a selective inhibitor of CYP2C enzymes, while the hydroxylations at the 8β-(Δ9-THC) position was highly inhibited by ketoconazole, a selective inhibitor of CYP3A enzymes. Human CYP2C9-Arg expressed in the microsomes of human B lymphoblastoid cells efficiently catalyzed the 11-hydroxylation of Δ9-THC (19.2 nmol/min/nmol CYP). Human CYP3A4 expressed in the cells catalyzed the 8β-hydroxylation (6.10 nmol/min/nmol CYP) and 9α,10α-epoxidation (1.71 nmol/min/nmol CYP) of Δ9-THC. These results indicate that CYP2C9 and CYP3A4 are major enzymes involved in the 11-hydroxylation and the 8-hydroxylation, respectively, of the cannabinoids by human hepatic microsomes.

- Available in vitro data doesn't suggest a potential for significant inhibition of CYP450 enzymes by dronabinol. Data is however, limited. While one study (Yamaori et al 2012) demonstrated that delta9-THC as a component of marijuana smoke potently inhibited CYP2C9 activity in vitro (measured using warfarin and diclofenac as probe substrates in human liver microsomes or rCYP2C9 incubations), the measured IC50 values ranging 1-4 μM (or 315 to 1200 ng/mL), appear markedly higher than the expected therapeutic concentrations of dronabinol following oral administration of SYNDROS (single dose Cmax of ~

1.5 ng/mL following a 4.25 mg dose), and hence did not appear to be clinically relevant.

- CYP2C9 polymorphism may impact dronabinol clearance. Approximately 2–3 fold higher dronabinol exposure was noted in individuals carrying genetic variants associated with diminished CYP2C9 function (Sachse-Seeboth et al, 2009).

- No specific investigations were identified in the literature that specifically evaluated potential CYP450 enzyme activation or induction effects of dronabinol. One published in vitro study identified a small dose-dependent activation of phenytoin hydroxylation in human liver microsomes in the presence of THC, or its metabolite (Bland et al., 2005). However, induction studies are usually carried out in human hepatocytes rather than human liver microsomes. In addition, the incubation duration of 30 minutes was very small. Therefore these findings were not considered for the label.

- Ketoconazole (400 mg once daily) increased AUC of THC (by 1.8-fold) and 11-hydroxy-delta 9-THC metabolite (by 3.5- fold). Rifampin (600 mg once daily) reduced AUC of THC (by 20-40 %) and 11-hydroxy THC (by 85 %). Due to differences in the drug product evaluated (a 1:1 combination oromucosal spray of THC and cannabidiol, CBD), dose, and route of administration (spray has potential for local absorption in the oral cavity), this information was not considered directly applicable for SYNDROS.

4.2 OCP filing memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**205525**	**Brand Name**	**SYNDROS**
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Dronabinol**
Medical Division	**DGIEP**	**Drug Class**	**Synthetic Cannabinoid**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**CINV and Anorexia in AIDS patients**
OCP Team Leader	**Sue Chih Lee, Ph.D.**	**Dosage Form**	**Oral Solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Anorexia: (b) (4) (2.125 mg) taken twice daily, before lunch and supper CINV: 4.25/m² given 1-3 h prior to chemotherapy, then every 2 to 4 h after chemotherapy is given, for a total of 4 to 6 doses/day**
Date of Submission	**06/01/2015**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**03/01/2016**	**Sponsor**	**Insys Therapeutics**
Medical Division Due Date	**03/01/2016 (secondary reviews)**	**Priority Classification**	**Standard**
PDUFA Due Date	**04/01/2016**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	**6**	**4**	**Reviewed: INS-08-008 INS-10-012 INS-12-015 INS004-15-059**
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**			
multiple dose:				

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**			**INS-06-006; uses an early syrup formulation**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**			**INS-08-008 IND-10-012 IND-12-015 (Pivotal)**
Food-drug interaction studies	**X**			**INS004-15-059 (submitted Jan 15, 2016)**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			**Agreed iPSP**
Literature References	**X**	**4**	**6**	**Sponsor submitted relevant literature was reviewed and additional papers were identified in support of metabolism and DDI information in label**
Total Number of Studies	**X**	**12**	**10**	**4 phase 1 trials and 6 publications**

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			505 b(2)
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			Literature and Marinol Labeling
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	X			RLD is Marinol Capsule
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			PK datasets
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	

	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Agreed iPSP
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

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

/s/

SANDHYA K APPARAJU
03/01/2016

SUE CHIH H LEE
03/01/2016