

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205525Orig1s000

MEDICAL REVIEW(S)

Clinical Review
Wen-Yi Gao, MD, PhD
NDA 205,525/000
Syndros (Dronabinol Oral Solution)

CLINICAL REVIEW

Application Type	Original NDA
Application Number(s)	NDA 205,525
Priority or Standard	Standard
Submit Date(s)	June 1, 2015
Received Date(s)	June 1, 2015
PDUFA Goal Date	April 1, 2016
Division/Office	Division of Gastroenterology and Inborn Errors Products/ODE3/CDER
Reviewer Name(s)	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	February 1, 2016
Established Name	Cannabinoid
(Proposed) Trade Name	Syndros
Applicant	Insys Therapeutics, Inc.
Formulation(s)	Oral Solution
Dosing Regimen	4.25 mg PO
Applicant Proposed Indication(s)/Population(s)	Treatment of anorexia associated with weight loss in patients with AIDS (acquired immune deficiency syndrome); and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatment.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as the Applicant proposed.

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Glossary

AC	advisory committee
AE	adverse event
AIDS	acquired immune deficiency syndrome
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GMRs	geometric mean ratios
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant Insys Therapeutics submitted an NDA of dronabinol aqueous formulation for the treatment of:

1. Anorexia associated with weight loss in patients with AIDS (acquired immune deficiency syndrome); and
2. Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

The established name of the to-be-marketed product is Dronabinol Oral Solution, and the proposed proprietary name is Syndros. Dronabinol Oral Solution belongs to the pharmacologic class of Cannabinoid.

The currently marketed dronabinol products are Marinol Capsules (2.5 mg, 5 mg and 10 mg in sesame oil; NDA 018651) which was approved in May 1985; and 3 generic dronabinol capsules (in soft gelatin capsule) which were approved in 2008, 2011, and 2014, respectively.

The Applicant found that the titration of Marinol effects is difficult. This could be due to: (1) the vehicle (sesame oil) was delivered unevenly to the absorption site (the epithelium of small intestine); and (2) complete absorption of dronabinol relies on complete absorption of the vehicle. As fatty acids, sesame oil needs to be water-solubilized by bile salts before its internalization. Thus, the Applicant developed an aqueous formulation (hydro-alcohol) that does not require bile salts for absorption. The Applicant stated that the new vehicle was able to evenly deliver dronabinol to the absorption site where it was absorbed rapidly. As a result, titration of Dronabinol Oral Solution becomes possible.

As per agreement with DGIEP at the End of Phase 2 meeting and the pre-NDA meeting, if the Applicant can provide the bioavailability/bridging study to Marinol Capsules, the approval of Dronabinol Oral Solution NDA would go through the 505(b)(2) regulatory pathway, and the Applicant did not need to conduct new efficacy studies. Efficacy of Dronabinol Oral Solution will rely on the bioavailability/bridging study of Marinol Capsules. On March 12, 2013, DGIEP reviewed the results of the second comparative bioavailability study using a lower dose (INS-12-015), and agreed that the results supported the bioequivalence.

Based on the bioequivalence, the Applicant proposed that:

- For appetite stimulation, Syndros (b) (4) (2.125 mg (b) (4) should be administered orally twice daily (bid), before lunch and supper. In the absence of significant adverse effects, the dosage may be gradually increased to a maximum of (b) (4) (17 mg/day) dosage of Syndros, administered in divided oral doses.

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- For antiemetic, (b) (4) (4.25 mg/m²), given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day. If the (b) (4) dose is not effective, and in the absence of significant side effects, the dose may be escalated by (b) (4) (2.125 mg/m²) increments to a maximum of (b) (4) (12.75 mg/m²) per dose.

The benefit-risk evaluation of Dronabinol Oral Solution shows that:

- The bioavailability was similar to Marinol Capsules. Thus, the to-be-marketed product qualifies for treatment of the above proposed indications.
- Dronabinol Oral Solution is given in aqueous solution, and is expected to mix well with the aqueous phase at the absorptive site.
- The absorption of new vehicle hydro-alcohol does not rely on bile salt secretion.
- As a result, the to-be-marketed product has less variation of therapeutic effectiveness than Marinol and is easier to titrate.

Safety assessments demonstrated that:

- The adverse event profile of Dronabinol Oral Solution 4.25 mg in the crossover pharmacokinetic trials included diarrhea, nausea, dizziness, headache and somnolence.
- These adverse events were similar to that of Marinol Capsules 5 mg. No new safety signals specific for the oral solution were identified.
- The Controlled Substance Staff (CSS) was consulted and determined that the Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, and presents a higher risk of unintentional overdoses, if abused. Accordingly, they recommend placing Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970). The Applicant conducted a comparative human abuse liability study (INS-13-017), Dronabinol Oral Solution was shown to have comparable abuse potential to that of Marinol.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In summary, the clinical reviewer recommends Approval of Dronabinol Oral Solution for the treatment of:

1. Anorexia associated with weight loss in patients with AIDS (acquired immune deficiency syndrome); and
2. Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Approval is based on the bioequivalence of Dronabinol Oral Solution to Marinol Capsules in the 505(b)(2) regulatory pathway.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The proposed oral solution dosage formulation (in alcohol) was developed as an alternative to dronabinol capsules (in sesame oil) to provide stable and titrate-able exposure to individual patients. Dronabinol Oral Solution 4.25 mg has been shown to be bioequivalent to Marinol Capsules 5 mg. Based on this demonstration of bioequivalence, Dronabinol Oral Solution is effective for the treatment of anorexia associated with weight loss in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed conventional therapies. These indications are recognized as effectively treated in the approved dronabinol labeling and supported by recent literature.

The adverse event profile of Dronabinol Oral Solution 4.25 mg has been shown in the crossover pharmacokinetic trials to include diarrhea, nausea, dizziness, headache and somnolence. These adverse events were similar to that of Marinol Capsules 5 mg. Labeled gastrointestinal, psychiatric and nervous system events were no different between these formulations, and no new safety signals specific for Dronabinol Oral Solution were identified. Analysis of postmarket safety reports from safety surveillance databases and the literature similarly has failed to identify any new potential safety signals. The Controlled Substance Staff (CSS) was consulted that the Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, and presents a higher risk of unintentional overdoses, if abused. Accordingly, they recommend placing Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970). Therefore, Dronabinol Oral Solution 4.25 mg is effective for the labeled dronabinol indications with an acceptable tolerability profile within subject variability, with an earlier appearance of detectable plasma dronabinol concentrations following administration relative to Marinol Capsules.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dronabinol Solution 4.25 mg (in alcohol) was studied in a single-dose, replicate crossover design comparative bioavailability study with Marinol Capsules 5 mg (in sesame oil) under fast conditions • The reference is Marinol Capsule 5 mg • Route of administration: oral • Population: healthy adults.	Dronabinol Solution 4.25 mg was bioequivalent to Marino Capsule 5 mg after oral administration to healthy adults under fast conditions. The data for the 11-OH-Δ9-THC metabolite also supported the bioequivalence of the two products. The supporting evidence is adequate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The PK parameters studied were Cmax, AUC(0-t), and AUC(inf).	
Current Treatment Options	- Marinol Capsules (sesame oil as vehicle); Approved in 1985 - Three generic dronabinol capsules (soft gelatin as vehicle); Approved in 2008, 2011, and 2014, respectively. - High variability in absorption and in clinical effectiveness	Dronabinol products are effective for the treatment of nausea and vomiting of CINV and anorexia of AIDS. Two placebo-controlled trials and one retrospective review supported the weight gain in AIDS patients (Bedi, 2010; Haney, 2007; DeJesus, 2007). A placebo-controlled study supported the treatment of nausea and vomiting in chemotherapy patients who have failed to respond adequately to conventional antiemetic treatment (Meiri, 2007).
Benefit	- Bioavailability similar to Marinol Capsules - It is given in aqueous solution, and is expected to be mixed well with the aqueous phase at the absorptive site. - Less variation of therapeutic effectiveness than Marinol - Easy to titrate	Dronabinol Oral Solution is more flexible for clinical uses.
Risk	- The adverse event profile of Dronabinol Oral Solution 4.25 mg in the crossover pharmacokinetic trials included diarrhea, nausea, dizziness, headache and somnolence. - These adverse events were similar to that of Marinol Capsules 5 mg. No new safety signals specific for the oral solution were identified. - The Controlled Substance Staff (CSS) concluded that the	The safety profile of Dronabinol Oral Solution is similar to that of Marinol Capsules. Analysis of postmarket safety reports from safety surveillance databases and the literature search support this conclusion.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, and presents a higher risk of unintentional overdoses, if abused. Accordingly, they recommend placing Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970).	
Risk Management	• The proposed use is directed to anorexia of AIDS patients or nausea and vomiting of cancer chemotherapy patients who have failed to respond adequately to conventional antiemetic treatment. • REMS (Risk Evaluation and Mitigation Strategy) is not required.	Two placebo-controlled trials and one retrospective review supported the safety in AIDS patients (Bedi, 2010; Haney, 2007; DeJesus, 2007). A placebo-controlled study supported the safety in chemotherapy patients (Meiri, 2007).

2 Therapeutic Context

2.1. Analysis of Condition

Disease Background and Scientific Rationale

1) Anorexia associated weight loss in HIV infected patients

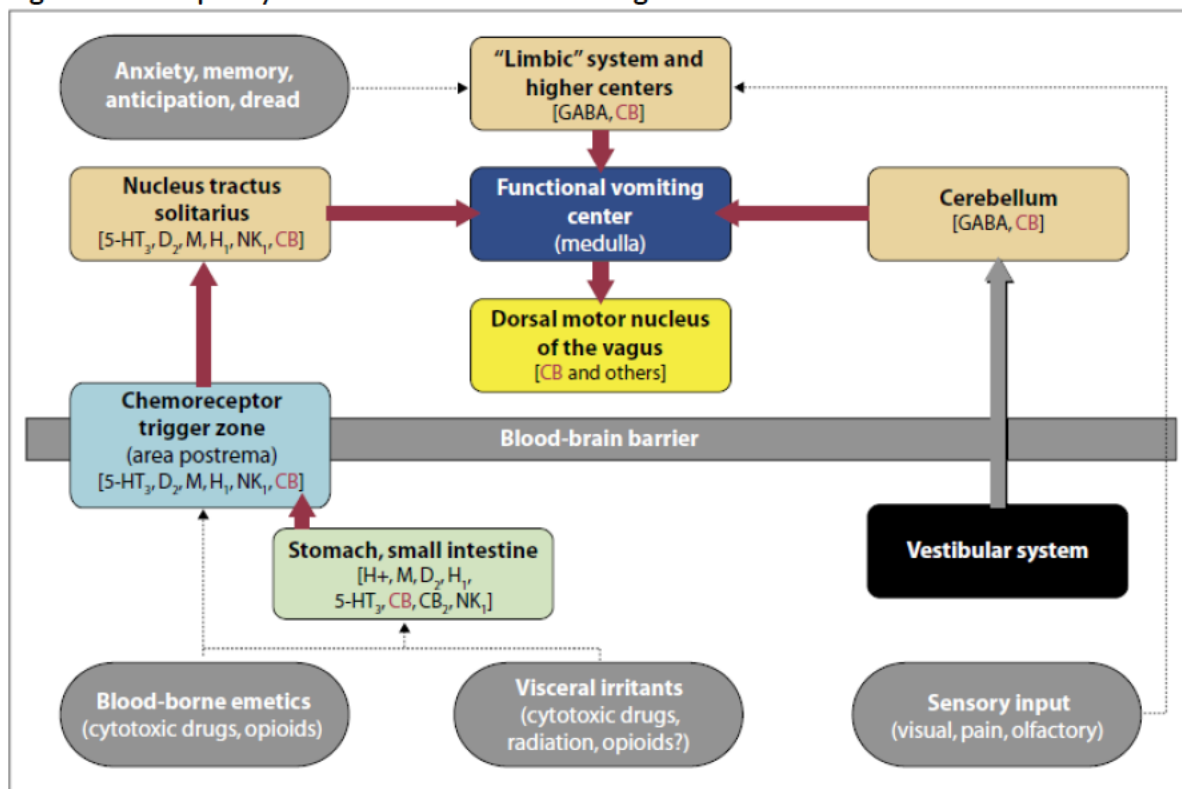
The etiology of anorexia associated with weight loss in HIV-infected patients is multifactorial. It includes HIV infection that reduces appetites; secondary opportunistic infection that reduces food intake; antimicrobial treatments that cause nausea and vomiting; painful oral and esophageal ulcers that reduce food intake; and HIV and opportunistic infections that cause chronic diarrhea and malabsorption.

HIV wasting syndrome is used to define AIDS illness. For example, unintentional weight loss of 10% over 12 months and a body mass index (BMI) < 20 kg/m² is one of the criteria of AIDS. In the era of HAART (highly active antiretroviral therapy), wasting is still a significant clinical complication in HIV infected patients. It has been estimated that the risk of death in an HIV-infected patient who loses 5% to 10% of baseline body weight may be as much as 2.5 times that of a patient who does not lose weight (Wheeler, 1999). Weight loss and malnutrition in HIV-infected patients can dramatically increase the morbidity associated with opportunistic infections. For these reasons, one major goal in the treatment of HIV/AIDS patients is to prevent weight loss. Many appetite stimulants (e.g., megestrol, cannabinoids, anabolic steroids, and recombinant human growth hormones) are currently used for this purpose.

2) Chemotherapy-induced nausea and vomiting (CINV)

The pathogenesis of CINV involves anti-cancer drug-induced release of multiple emetic transmitters, such as dopamine, serotonin, and substance P (NK1-receptor). The chemoreceptors are located at the GI tract and the 4th ventricle of CNS, "Area postrema". The signal is transmitted to the vomiting center located in the medulla, triggering vomiting reflex. The hypothesis is that different neuromodulators may preferentially mediate nausea and emesis. It was reported that the serotonin and substance P (NK1) are most active in mediating emesis; while dopamine and cannabinoids are most active in mediating nausea. In Figure 1, CB denotes cannabinoid receptor. The receptors are distributed at both the peripheral and CNS tissues.

Figure 1: Multiple Systems Involved in the Pathogenesis of CINV



Cited from Slatkin NE. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: Beyond prevention of acute emesis. Presented at the 2006 Chicago Supportive Oncology Conference, Chicago, Illinois. www.SupportiveOncology.net
 Abbreviations: GABA = gamma-aminobutyric acid; CB = cannabionid; 5-HT₃ = 5-hydroxytryptamine₃ (serotonin); NK = neurokinin; M = muscarine; D = dopamine; H = histamine; H⁺ = hydrogen ion.

2.2. Analysis of Current Treatment Option

1) Current Medical Treatment of CINV

There are 5 major classes of antiemetic agents commonly used for treating CINV (Table 1):

- Serotonin (5-HT₃) receptor antagonist is the most frequently used antiemetic class. These drugs are well tolerated, but are associated with QT-interval prolongation. IV dolasetron is not recommended for the prevention of CINV due to a potential increased risk for cardiac arrhythmias.
- The neurokinin (NK1) antagonists are the newest class for CINV. Aprepitant (Emend), the first drug in this class, is used in conjunction with a corticosteroid to prevent CINV associated with high-risk regimens. Aprepitant is a major substrate of cytochrome P450 (CYP) 3A4, and has clinically significant drug-drug interactions with CYP 3A4 inhibitors,

inducers, and other substrates.

- Corticosteroids are among the oldest agents used in prevention of CINV, and they remain a backbone of therapy. They are highly effective at preventing delayed CINV and they increase the effects of other antiemetic agents. Dexamethasone is the preferred corticosteroid for antiemetic regimens, due to ease of dosing and predictable outcomes. Common adverse effects of short-term use include hyperglycemia and hypertension; long-term use may result in immunosuppression.
- The dopamine antagonists were historically the first choice for preventing CINV. However, effective prevention requires high doses of these agents and therefore is limited by increased incidence of extrapyramidal reactions associated with the drugs.
- The first cannabinoid, Marinol, was approved in 1985. It has a different safety and effectiveness profile when compared with other existing classes. It appears that cannabinoids are more active in mitigating nausea compared to other types of antiemetic agents.

Table 1: Summary of Commonly Used Antiemetic Agents

Product Name	Relevant Indication	Year of Approval	Dosing	Common AEs	Other Comments
Neurokinin antagonists					
Aprepitant/ Fosaprepitant (Emend, Merck)	High emetic risk	2008	PO: 125 mg, Day 1; 80 mg, Days 2-3	Fatigue, hiccups, weakness	Caution with severe hepatic impairment
Serotonin antagonists					
Dolasetron (Anzemet, Sanofi-aventis)	High- and moderate-risk	1984	PO: 100 mg, Day 1; PRN Days 2-3	Constipation, diarrhea, fatigue, headache	Risks of QTc prolongation
Granisetron	Same as above	1993	PO: 1 mg, Day 1; PRN Days 2-3 IV: 0.01 mg/kg, Day 1 Transdermal: 24 h before chemotherapy	Same as above	Same as above
Ondansetron	Same as above	1991	PO: 24 mg, Day 1; 8 mg bid PRN, Days 2-3 IV: 8 mg or 0.15 mg/kg	Same as above	Same as above
Palonosetron (Aloxi, Eisai)	Same as above	2003	IV: 0.25 mg once	Same as above	Same as above
Corticosteroids					
Dexamethasone	High-, moderate-risk	N/A	High-risk dosing: 12 mg, Day 1; 8 mg, Days 2-4 Moderate-risk: 8-12 mg, Days 1-3	Hypertension, hyperglycemia, immune and adrenal suppression	CYP 3A4 inhibitor and inducer
Dopamine receptor antagonists					
Metoclopramide	Adjunctive	1979	PO/IV: 10-40 mg q4-6h PRN	Dystonia, drowsiness,	Dyskinesia, cardiac

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				restlessness, diarrhea	arrhythmias
Prochlorperazine	Adjunctive	1956	PO/IV: 10 mg q4-6h PRN	Anticholinergic, extrapyramidal symptoms QTc prolongation	Same as above
Cannabinoids					
Dronabinol	Adjunctive	1985	PO: 5-10 mg q3-6h	Abnormal thinking, paranoia	Caution in elderly patients

From the reviewer's notes based on Thompson et al. Chemotherapy-induced nausea and vomiting. Pharmacy Practice News. 2013: 19-23.

2) Current Medical Treatment of Anorexia in HIV-infected Patients

Many appetite stimulants (e.g., megestrol, cannabinoids, anabolic steroids, and recombinant human growth hormones) are currently used for this purpose.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dronabinol is the active moiety of Marinol Capsules (NDA 18651) that was approved and marketed in the U.S. on May 31, 1985. Also, generic dronabinol capsules (ANDA 78292, ANDA 78501, and ADNA 79217) were approved on June 27, 2008, August 19, 2011, and June 20, 2014, respectively.

On December 20, 2005, Solvay Pharmaceuticals (Marinol Capsules) proposed to revise the label based on the safety data (Periodic Update Report) submitted in July 2005. The Division of Drug Risk Evaluation (DDRE) conducted an independent review using the Adverse Event Reporting System (AERS) from the period of approval to February 9, 2006. DDRE identified 45 cases of serious adverse events. Twenty seven (27) cases were available for DDRE review. DDRE found one fatality: An 88-year-old male who was participating in a study evaluating the use of dronabinol to treat agitation associated with Alzheimer's disease (patient received 10 mg of dronabinol a day for 36 days). He fell and experienced a fatal intracerebral hemorrhage.

Half of the adverse events identified in the DDRE report were neurologic or psychiatric in nature. Of the 7 neurologic adverse events, 6 cases involved seizures and 1 involved stupor. Most of the cases were likely associated with an underlying seizure history or recent stroke history (two cases provided insufficient information to make a determination [one of these patients had underlying Alzheimer's disease]). Psychiatric events included altered mental

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status, confusion, delirium, hallucinations, and “homicidal” behavior; 7 patients were hospitalized and 1 case was reported as life threatening. With the exception of seizure, the neurologic and psychological adverse events are labeled. Out of 27 cases, 3 patients who took dronabinol experienced falls and fractures, including 1 fatality. The age of the 3 patients ranged from 88 to 92 years old.

DDRE concluded that the Marinol label should include:

- A warning about use of this drug in elderly, with an emphasis on recommending a lower starting dose.
- Although seizure was reported in patients who had an underlying history of seizure, the role of dronabinol could not be ruled out.

The DGIEP Medical Reviewer Ann Marie Trentacosti, MD recommended at the time:

- The Warnings and Precaution section should remove the sentence “in antiemetic studies, no difference in tolerance was apparent in patients >55 years old”.
- The labeling revision “the role of dronabinol in seizure could not be ruled out” by DDRE and the Applicant is acceptable.
- The inclusion of safety concerns in the elderly by the Applicant in the Warnings and Precaution is adequate.

Medical Officer Comment:

These recommendations have been incorporated into the Marinol Capsules labeling.

3.2. Summary of Presubmission/Submission Regulatory Activity

Development of Dronabinol Oral Solution was under IND 785228:

- The IND was submitted on June 14, 2006.
- End of phase 2 meeting was held on May 13, 2010. In the meeting, DGIEP advised that the sponsor-proposed scaled bioequivalence method was not acceptable. The sponsor needs to conduct a bioavailability study; if it fails, the sponsor needs to conduct clinical studies. In addition, the sponsor should conduct a food effect study for the proposed product. DGIEP also advised that the sponsor should formulate a pediatric clinical development plan to meet the requirement of PREA (the Pediatric Research Equity Act).
- Pre-NDA meeting was held on April 17, 2012. Study report of INS-10-012 did not support the bioequivalence. DGIEP advised the sponsor to provide safety data of the proposed product. Since Dronabinol Oral Solution is not formulated in sesame oil as Marinol (Schedule III), it was also recommended that the abuse potential of the proposed product be studied. DGIEP reiterated the PREA Requirements.
- On March 12, 2013, DGIEP reviewed the results of additional comparative bioavailability study using a lower dose. The Division agreed that the result supported

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the bioequivalence.

- On December 17, 2013, DGIEP provided comments on Human Abuse Potential Study Protocol. DGIEP also advised that the proposed formulation may require a REMS to ensure that the benefits of the drug out-weigh its risks.
- On August 12, 2014, NDA 205525 was received by FDA.
- On October 10, 2014, DGIEP advised that Refuse to File action was taken, because of the failure to address requirements under PREA.
Also, DGIEP requested the Applicant address: Reports of syncope that have occurred after the approval of Marinol.
- On May 19, 2015, DGIEP agreed with the submitted iPSP.
- On June 1, 2015, the Applicant re-submitted NDA 205525. The submission contains 4 clinical pharmacology studies and 1 human abuse potential study.

3.3. Foreign Regulatory Actions and Marketing History

The Applicant of Dronabinol Oral Solution did not have a foreign marketing application.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of New Drug Bioequivalence Evaluation (DNDBE) and the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection of the clinical or analytical sites (8/4/2015), because OSIS recently inspected the sites and classified them as No Action Indicated (NAI) (Review of Shila NKah in DARRTS, 8/4/2015).

Request for Inspection of Biopharmaceutical Site

Study Number INS-12-015

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

Clinical Site

Worldwide Clinical
Trials Drug Development Solutions,
Clinical Research Services (WCTCRS)
2455 N.E. Loop 410, Suite 150
San Antonio, TX 78217

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(Tel) 210-635-1500
Clinical Investigator: Joe Juren, M.D.

Analytical Site



4.2. Product Quality

The Quality Review Team consisted of the following disciplines and reviewers:

- Drug Substance: Reviewer Jeffery Medwid, ONDP/DND/API;
- Drug Product: Reviewer Hitesh Shroff, ONDP/DND/NDPBV;
- Process: Reviewers Kelly Forney-Stevens and Peter Krommenhoek, OPF/DPAIII;
- Microbiology: Reviewer Jonathan Swoboda, OPF/DMA;
- Facility: Reviewer Vipul Dholakia, OPF/DMA;
- Biopharmaceutics: Reviewer Peng (Vincent) Duan, ONDP/DB;
- ORA lead: Paul Perdue Jr. ORA/OMPTO;
- Environmental Assessment: Reviewer Hitesh Shroff, ONDP/DND/NDPBV

The review team had the following recommendation and conclusions:

The Applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. The Office of Facility and Process has made a final overall manufacturing Inspection “Approval” recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted. However, the label/labeling issues have *not* been completely resolved as of this review and the device consult review from the Office of Compliance, CDRH is still pending. Therefore, from the OPQ perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) and 21 CFR 314.125(b)(13), until the above issues are satisfactorily resolved (Dronabinol OPQ review signed copy, 2/29/2016)

4.3. Clinical Microbiology

Clinical microbiology study was not conducted in this submission.

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4.4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology/Toxicology study of Dronabinol Oral Solution was not conducted at the time of NDA submission. The to-be-marketed product was demonstrated to be bioequivalent to the reference Marinol Capsules (NDA 18,651). In the original Marinol Capsule NDA, the Pharmacology/Toxicology studies included:

- Acute toxicity studies of Delta-9 ^{(b) (4)}-tetrahydrocannabinol (Delta-9-THC) after single oral and Intravenous doses to rats, monkey and dogs.
- Subacute toxicity studies of Delta-9-THC and ^{(b) (4)} PO in Fisher rats, rhesus monkeys for 28 days.
- Chronic studies toxicity studies of Delta-9-THC and ^{(b) (4)} PO in fisher rats for 119 days.
- Reproduction and hormonal studies of Delta-9-THC PO in rats, mices, and rabbits.
- Cytogenetic studies of single oral doses of Delta-9-THC PO on female Sprague Dawley rats.

There was no disagreement of approval by the pharmacology and toxicology team.

4.5. Clinical Pharmacology

The clinical pharmacology findings are summarized as follows:

Dronabinol Oral Solution 4.25 mg was bioequivalent to Marinol Capsule 5 mg under fasted conditions in healthy adults based on the values of C_{max}, AUC(0-t), and AUC(inf). The data from the Delta-9-THC metabolite also support the bioequivalence of the two products (see Section 6.1 for details).

There was no disagreement of approval by the clinical pharmacology team.

4.5.1. Mechanism of Action

The pathogenesis of nausea and vomiting is initiated by exposure to various chemical substances. These substances stimulate the receptors located at the GI tract and the 4th ventricle of CNS, "Area postrema". The exciting signal is transmitted by different neurons that release emetic neurotransmitter, such as dopamine, serotonin, and substance P (NK1-receptor). The signal is then transmitted to the vomiting center in the medulla, triggering vomiting reflex (Figure 1).

Cannabinoid receptor is also distributed in both peripheral tissues (stomach and small intestine) and central nerve system (chemoreceptor trigger zone of the 4th ventricle, nucleus tractus solitarus, vomiting center in the medulla, cerebellum, and cerebral cortex limbic sytem).

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Endogenous cannabioids play an inhibitory role in response to overstimulation of postsynaptic nerves. Exogenous cannabinoids mimic the inhibitory effects against the exciting presynaptic nerves.

It is proposed that the serotonin and substance P (NK1) are most active in mediating emesis; while dopamine and cannabinoids are most active in mediating nausea.

4.5.2. Pharmacodynamics

Pharmacodynamic study was not required at the pre-NDA meeting with DGIEP.

4.5.3. Pharmacokinetics

The human PK parameters were studied in INS-12-015. Under the fast conditions, the key PK parameters are as follows:

Dronabinol Oral Solution:

$C_{max} = 1.95 \pm 1.28$ ng/mL; $AUC(0-t) = 3.53 \pm 1.87$ h x ng/mL; $AUC(inf) = 3.84 \pm 1.80$ h x ng/mL; $t_{1/2} = 5.58 \pm 2.66$ h

Marinol:

$C_{max} = 2.41 \pm 1.60$ ng/mL; $AUC(0-t) = 3.99 \pm 2.51$ h x ng/mL; $AUC(inf) = 4.05 \pm 2.50$ h x ng/mL; $t_{1/2} = 3.07 \pm 2.64$ h

Dronabinol Oral Solution 4.25 mg was bioequivalent to Marinol Capsule 5 mg under fasted conditions in healthy adults based on the values of C_{max} , $AUC(0-t)$, and $AUC(inf)$. The data from the Delta-9-THC metabolite also supports the bioequivalence of the two products (Section 6.1 for details).

4.6. Devices and Companion Diagnostic Issues

There was no diagnostic device included in this application. CDRH reviewed the oral dispenser and container. The review team (Kathleen Fitzgerald and Alan Stevens) commented that (b) (4) oral dispenser is suitable for Dronabinol Oral Solution and allows accurate dispensing of the product. CDRH final recommendation: The Applicant has adequately addressed all CDRH deficiency questions. The reviewer does not believe that use of the device will result in a toxicological response (2/29/2016).

4.7. Consumer Study Reviews

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There was no consumer study review in this submission.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

No clinical efficacy and safety studies were conducted.

5.2. Review Strategy

This is a 505(b)(2) application, and a specific efficacy and safety study was not conducted. The clinical pharmacology study INS 12-015 was used to support the bioequivalence between Dronabinol Oral Solution and Marinol Capsules.

In addition, literature was reviewed. Dronabinol products were effective and tolerable for the treatment of nausea and vomiting of CINV and anorexia of AIDS. Two placebo-controlled trials and one retrospective review supported the indication of weight gain in AIDS patients (Bedi, 2010; Haney, 2007; DeJesus, 2007). A placebo-controlled study supported the treatment of nausea and vomiting in chemotherapy patients (Meiri, 2007).

6 Review of the PK Trial Used to Support Bioequivalence between Dronabinol Oral Solution 4.25 mg and Marinol Capsules 5 mg

6.1. Study INS-12-015

6.1.1. Study Design

Overview and Objective

Study Title: “A Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 4.25 mg Versus Marinol 5 mg Capsules Under Fasted Conditions”

The primary objective of this study was to compare the oral bioavailability of the to-be-marketed formulation, Dronabinol Oral Solution, 4.25 mg to that of Marinol Capsule 5 mg in healthy subjects under fasting conditions.

Trial Design

This was an open-label, 2-treatment, 4-period, single-dose, randomized crossover study of the comparative bioavailability of Dronabinol Oral Solution 4.25 mg (Insys Therapeutics, Inc.) and Marinol Capsules 5 mg (Unimed Pharmaceuticals). Fifty-two (52) healthy male and female volunteers were randomly assigned to 1 of 2 treatment sequences, Sequence 1 (T → R → T → R) or Sequence 2 (R → T → R → T), where T = the test product, Dronabinol Oral Solution, and R = the reference product, Marinol Capsules. Subjects received one dose of the dronabinol formulation after an overnight fast; and there was a minimum 7-day washout between the dosing in Periods 1 through 4.

The 52 subjects were randomized into 2 groups. Group 1 consisted of Subject IDs #201 through #226 and Group 2 consisted of Subject IDs #227 through #252. Blood samples for the measurement of dronabinol and 11-OH- Δ^9 -THC were collected before (pre-dose) and after the initiation 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 hours post-dose.

Study Efficacy Endpoints

No efficacy evaluation was performed in this study.

Statistical Analysis Plan

All statistical analyses were performed using SAS® for Windows Version 9.3.

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Primary Analysis

Comparison of the PK parameters C_{max}, AUC(0-t), and AUC(inf) for dronabinol and 11-OH-Δ⁹-THC between the test and reference formulations was performed according to a linear mixed effects statistical model where the sequence, treatment, period, and group were as the fixed effects and subject as a random effect. The results were calculated using the natural logarithms method. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were constructed for the treatment ratios (Dronabinol Solution-to-Marinol Capsule) of all three parameters using the natural log transformed data and the two-one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. Equivalence was to be concluded if the confidence intervals for the three parameters are within the limits of 80.00% to 125.00%.

Secondary Analysis

If the 90% CI for a parameter [C_{max}, AUC(0-t), and/or AUC(inf)] from the primary analysis was not contained within 80.00% to 125.00%, the within-subject standard deviation (s_{WR}) was $\geq$ 0.294 for a parameter, and the GMR (Geometric mean ratio) was between 80.00% and 125.00%, then the comparative bioavailability of that parameter was assessed using the reference-scaled bioequivalence procedure.

Safety Evaluation

Safety parameters: physical examinations, vital signs, clinical laboratory evaluations, ECGs, concomitant medications assessments, and reported or observed adverse event assessments.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has attested that all the 5 studies (INS-06-006, INS-08008, INS-10-012, INS-12-015, and INS-13-017) submitted to this NDA were conducted in accordance with good clinical practice (GCP), that includes the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70). The studies were performed under IND 75,228.

Financial Disclosure

The Applicant has adequately disclosed financial interests or arrangements with the clinical investigators (see Appendix 13.2). The Applicant stated that none of the clinical investigators received significant payments as defined in 21 CRG 54.2(a), (b), and (f).

Medical Officer Comments:

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The Applicant has reasonably disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not raise concerns which would possibly jeopardize the integrity of the data.

Demographic Characteristics of Study INS-12-15

A total of 52 adult subjects were enrolled in the study. There were 28 females and 24 males. The ages ranged from 18 to 53 years of age, and their BMI ranged from 21.0 to 29.9 kg/m². Other demographic data are presented in the table below.

Table 2: Summary of Demographic Data

Characteristic	Statistic	Completed	Enrolled
Age (years)	Number of Subjects	50	52
	Mean	33	33
	SD	10	10
	Median	31	31
	Range	18 - 53	18 - 53
Gender	Number of Subjects n(%)	50	52
	Female	27 (54.00%)	28 (53.85%)
	Male	23 (46.00%)	24 (46.15%)
Ethnicity ^a -Race	Number of Subjects n(%)	50	52
	H/L-American Indian/Alaska Native	4 (8.00%)	4 (7.69%)
	H/L-White	23 (46.00%)	24 (46.15%)
	NH/L-American Indian/Alaska Native	1 (2.00%)	1 (1.92%)
	NH/L-American Indian/Alaska Native, Black, White	1 (2.00%)	1 (1.92%)
	NH/L-Asian	1 (2.00%)	1 (1.92%)
	NH/L-Black	9 (18.00%)	10 (19.23%)
	NH/L-White	11 (22.00%)	11 (21.15%)
BMI ^b (kg/m ²)	Number of Subjects	50	52
	Mean	25.5	25.4
	SD	2.4	2.4
	Median	25.8	25.7
	Range	21.0 - 29.9	21.0 - 29.9
Height (cm)	Number of Subjects	50	52
	Mean	166.6	166.8
	SD	9.6	9.7
	Median	167.5	167.5
	Range	145.0 - 188.0	145.0 - 188.0
Weight (kg)	Number of Subjects	50	52
	Mean	70.8	70.9
	SD	10.1	10.1
	Median	69.6	69.6
	Range	52.7 - 94.6	52.7 - 94.6

^a H/L = Hispanic or Latino, NH/L = Not Hispanic or Latino

^b BMI = Body Mass Index

Program name: Summary of Demographic.sas (06DEC12:14:12:29)

Source: Demographic Data (Protocol # INS-12-015)

Test Product

Dronabinol Oral Solution (4.25 mg/0.85mL)

Dose = 1 x (4.25 mg/0.85mL) oral solution

Reference Product

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Marinol Capsules 5 mg
Dose = 1 x 5 mg capsule, orally administered

Duration of Treatment

Four single-dose treatments were administered with a seven-day washout period between doses.

Pharmacokinetic Results

1) Dronabinol

Within each formulation, there was good concordance between replicates with respect to the mean plasma dronabinol concentrations and PK parameters. The mean plasma concentrations after administration of the Solution were comparable to those for the Marinol Capsule and this is also true for most of the individual subject graphs.

The mean pharmacokinetic parameters for the 2 formulations with both replicates combined are compared in the following table:

Table 3: Comparison of PK parameters for dronabinol with single dose of Dronabinol Solution 4.25 mg and Marinol Capsule 5 mg in healthy adults under fast conditions

Parameter*	Insys Lot No. 100310 (Test)	Marinol Lot No. 277967A (Reference)
C _{max} (ng/mL)	1.95 ± 1.28 (101)	2.41 ± 1.60 (101)
T _{max} (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)
λ _z (1/h)	0.1488 ± 0.0675 (91)	0.3271 ± 0.1555 (86)
t _{1/2} (h)	5.58 ± 2.66 (91)	3.07 ± 2.64 (86)

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

The two formulations were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf). The statistical analysis and comparison were shown in Table 4.

Table 4: Statistical comparison of PK parameters for dronabinol after Dronabinol Solution 4.25 mg and Marinol Capsule 5 mg under fast conditions

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Parameter	Least Squares Geometric Means		Geometric Mean Ratio (%)*			Within-Subject Standard Deviation†		
	Insys Lot No. 100310	Marinol Lot No. 277967A	Estimate	90% Confidence Interval		Insys Lot No. 100310	Marinol Lot No. 277967A	
	Insys Lot No. 100310 vs. Marinol Lot No. 277967A							
C _{max}	1.62	1.97	82.50	74.62	→	91.22	0.321	0.364
AUC(0-t)	3.12	3.32	94.07	84.59	→	104.61	0.186	0.426
AUC(inf)	3.45	3.43	100.39	89.47	→	112.65	0.167	0.453

*Based on analysis of natural log-transformed data. Lower confidence limits < 80.00% and upper confidence limits > 125.00% are shown in red.

†Values ≥ 0.294 are shown in red.

2) 11-OH-Δ9-THC

There was reasonable concordance between replicates with respect to the mean plasma concentrations of 11-OH-Δ9-THC and the PK parameters. The overall mean plasma concentrations after administration of the Solution and Capsule were slightly lower; this is also apparent from examination of the individual subject graphs.

The arithmetic mean values for C_{max}, AUC(0-t), and AUC(inf) were lower for the Solution than the Capsule. The GMRs (Geometric mean ratios) ranged from 77.33% to 83.92% and the lower limits of the associated 90% CIs were < 80% as shown in Table 5. The statistical analysis and comparison were shown in Table 6.

Table 5: Comparison of PK parameters for 11-OH-Δ9-THC with single dose of Dronabinol Solution 4.25 mg and Marinol Capsule 5 mg in healthy adults under fast conditions

Parameter*	Insys Lot No. 100310 (Test)	Marinol Lot No. 277967A (Reference)
C _{max} (ng/mL)	2.77 ± 1.48 (101)	3.63 ± 2.19 (101)
T _{max} (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)
λ _z (1/h)	0.0716 ± 0.0452 (97)	0.0708 ± 0.0583 (97)
t _{1/2} (h)	11.7 ± 4.01 (97)	11.9 ± 3.89 (97)

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

Table 6: Statistical comparison of PK parameters for 11-OH-Δ9-THC after Dronabinol Solution 4.25 mg and Marinol Capsule 5 mg under fast conditions

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Parameter	Least Squares Geometric Means		Geometric Mean Ratio (%) [*]				Within-Subject Standard Deviation [†]	
	Insys	Marinol	Geometric Mean Ratio (%) [*]				Insys	Marinol
	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								
C _{max}	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

^{*}Based on analysis of natural log-transformed data. Lower confidence limits < 80.00% and upper confidence limits > 125.00% are shown in red.
[†]Values ≥ 0.294 are shown in red.

As discussed with the Division at the End of Phase 2 meeting, these data supported the bioequivalence between Dronabinol Oral Solution and Marinol Capsules.

Conclusion

The Applicant Insys Therapeutics stated that Dronabinol Solution 4.25 mg was bioequivalent to Marino Capsule 5 mg after oral administration to healthy adults under fasting conditions. The PK parameters studied were C_{max}, AUC(0-t), and AUC(inf) for Dronabinol. The data for the 11-OH-Δ9-THC metabolite also supported the bioequivalence of the two products.

Medical Officer Comments:

The clinical reviewer agrees that the PK data support the conclusion of bioequivalence between Dronabinol Oral Solution and Marinol.

Dose/Dose Response

No dose response study was conducted.

Durability of Response

No durability of response study was conducted.

Persistence of Effect

Persistence of effect of the product was not performed.

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy Trial

There was no efficacy study conducted.

8 Review of Safety

8.1. Safety Review Approach

Dronabinol Oral Solution is intended for anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. A comparative pharmacokinetic study showed bioequivalence between Dronabinol Oral Solution 4.25 mg and Marinol Capsules 5 mg (INS-12-015). Dronabinol Oral Solution and a related formulation Dronabinol Oral Syrup have been studied in five pharmacokinetic studies in healthy adults. The safety review is based on the following five studies:

- A single-dose, placebo-controlled, sequential ascending dose study of Dronabinol Oral Syrup (INS-06-006)
- A single-dose comparative study of Dronabinol Oral Syrup vs. Dronabinol Oral Solution vs. Marinol Capsules (INS-08-008)
- A single-dose comparative study of Dronabinol Oral Solution vs. Marinol Capsules (INS-10-012)
- A pivotal randomized, two-sequence, replicate crossover trial of Dronabinol Oral Solution vs. Marinol Capsules (INS-12-015)
- A single-dose, randomized, six-sequence, three-period, crossover trial of Dronabinol Oral Solution vs. Marinol Capsules under fed and fasted conditions in healthy volunteers (INS-004-15-059)

In addition to these pharmacokinetic studies, a human abuse liability study (INS -13-017) was conducted in recreational cannabinoid users. Adverse events and the abuse-related findings from INS-13-017 are included as a separate section because subjects are recreational drug users not considered to be representative of the indicated patient population and were exposed to supratherapeutic doses (10 mg or 30 mg).

The following Table provides a summary of the four pharmacokinetic studies and one human abuse liability study relevant to the safety of Dronabinol Oral Solution.

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Table 7: Dronabinol Oral Solution Clinical Safety Database

Study Number	Phase	Indication and Population	Study Design	Dosing Scheme
INS-06-006	PK/1	Healthy subjects	Single center, randomized, single-blind, placebo controlled sequential ascending dose, 4 sequence	In each study period, subjects received three of four doses of Dronabinol Syrup and one dose of placebo. Dronabinol Syrup 2.5 mg (5 mg/mL, 0.5 mL) Dronabinol Syrup 2.5 mg (5 mg/mL, 0.5 mL) with 240 mL water Dronabinol Syrup 5 mg (5 mg/mL, 1 mL) Dronabinol Syrup 10 mg (5 mg/mL, 2 mL) Placebo Syrup
INS-08-008	PK/1	Healthy subjects	Three period, three sequence crossover	Two prospective Dronabinol Oral 10 mg formulations (Oral Syrup 10 mg and Oral Solution 10 mg) Marinol® Capsules 10 mg
Study Number	Phase	Indication and Population	Study Design	Dosing Scheme
INS-10-012	PK/1	Healthy subjects	Pivotal, open-label, randomized, four period, two treatment, two sequence replicate, crossover	Dronabinol Oral Solution 5 mg (1 mL, 5 mg/mL) Marinol® Capsules 5 mg
INS-12-015	PK/1	Healthy subjects	Pivotal, open-label, randomized, four period, two treatment, two sequence replicate, crossover	Dronabinol Oral Solution 4.25 mg (0.85 mL, 5 mg/mL) Marinol® Capsules 5 mg
INS-13-017	Abuse liability/1	Recreational cannabinoid users	Single-dose, randomized, double-blind, double-dummy placebo- and active-controlled, 5-way crossover study	Dronabinol Oral Solution 10 mg and Placebo Capsules Dronabinol Oral Solution 30 mg and Placebo Capsules Marinol® 10 mg Capsules and Placebo Oral Solution Marinol® 30 mg Capsules and Placebo Oral Solution Placebo Oral Solution and Placebo Capsules

From the NDA submission, Section 5.3.5.3 Integrated Summary of Safety.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Dronabinol exposures in the four pharmacokinetic studies (INS-06-006, INS-08-008, INS-10-012, INS-12-015) and in the human abuse liability study (INS-13-017) are summarized in Table 8 and Table 9, respectively. Dronabinol exposures for studies INS-10-012 and INS-12-015 have been presented as total administered doses taking into account that most subjects in each of these 2-sequence replicate dosing crossover trials received two separate doses of each test formulation. Subjects were exposed to Marinol Capsules 5 mg the most (273 exposures), followed by Dronabinol Oral Solution 5 mg (169 exposures) and Dronabinol Oral Solution 4.25 mg (101 exposures).

Table 8: Summary of Exposure to Study Drug in Pharmacokinetic Studies

	Dronabinol Oral Solution 4.25 mg	Dronabinol Oral Solution 5 mg	Dronabinol Oral Solution 10 mg	Dronabinol Oral Syrup 2.5 mg	Dronabinol Oral Syrup 5 mg	Dronabinol Oral Syrup 10 mg	Marinol® Capsules 5 mg	Marinol® Capsules 10 mg	Placebo
INS-06-006				48	23	23			31
INS-08-008			18			18		18	
INS-10-012		169 ^b					171 ^b		
INS-12-015	101 ^b						102 ^b		
Total	101	169	18	48	23	41	273	18	31

^a Some subjects received Dronabinol Oral Syrup 2.5 mg twice during their dosing schedule. Those patients that received Dronabinol Oral Syrup twice were dosed in different manners during the study (with or without 240 mL of water).

^b The clinical study report presented numbers of subjects taking study medications in the Safety Data Tables and Figures, as total treatments across the replicate dosing schedule. Exposure data here are provided as in the clinical study report (INS-10-012 and INS-12-015).

Dronabinol exposure in Study INS-004-15-059 is summarized as follows:

Fifty-four subjects enrolled were administered all scheduled doses of dronabinol oral solution and Marinol capsule. Three study periods were Treatment A = Dronabinol Oral Solution, 4.25 mg, under fed conditions; Treatment B = Marinol Capsule, 5 mg, under fed conditions; and Treatment C = Marinol Capsule, 5 mg under fasted conditions. Dosing in the 3 study periods was separated by a 7-day washout period. The total dose administered to each subject who completed all 3 study periods was 14.25 mg of Dronabinol.

Table 9: Summary of Exposure to Study Drug in the Human Abuse Liability Study (INS-13-017)

Dronabinol Oral Syrup 10 mg	Dronabinol Oral Syrup 30 mg	Marinol® Capsules 10 mg	Marinol® Capsules 30 mg	Placebo
36	40	35	37	39

Source: INS-13-017 Final Clinical Study Report, Table 19

8.2.2. Relevant characteristics of the safety population:

This is a 505(b)(2) New Drug Application for the treatment of nausea and vomiting associated with cancer chemotherapy and anorexia associated with weight loss in AIDS patients. The bioequivalent studies were conducted with the healthy adults.

The demographics of the studies (INS-06-006, INS-08-008, INS-10-012, and INS-12-015) are summarized in Table 10. Subjects were all adults excluding the elderly, and were predominantly White.

There were no significant differences in the demographic variables in the studies.

Table 10: Demographics and Baseline Characteristics, Safety Population

	INS-06-006	INS-08-008		INS-10-012		INS-12-015		INS-13-017
	Completed n=31 Enrolled n=32	Completed n=18	Enrolled n=18	Completed n=82	Enrolled n=88	Completed n=50	Enrolled n=52	Completed n=33 Enrolled n=43
Age (years)								
Mean (SD)	34.0 (±13.1)	34 (8)	34 (8)	33 (11)	33 (11)	33 (10)	33 (10)	36.0 (8.84)
Median		35	35	30	30	31	31	
Range		24-49	24-49	18-55	18-55	18-53	18-53	21-55
Gender								
Male	16 (50.0%)	12 (66.67%)	12 (66.67%)	47 (57.32%)	51 (57.95%)	23 (46.0%)	24 (46.1%)	37 (86.0%)
Female	16 (50.0%)	6 (33.33%)	6 (33.33%)	35 (42.68%)	37 (42.05%)	27 (54.0%)	28 (53.8%)	6 (14.0%)
Race								
Caucasian	30 (93.8%)	7 (38.89%)	7 (38.89%)	25 (30.49%)	27 (30.68%)	11 (22.0%)	11 (21.1%)	32 (74.4%)
Black/African American		2 (11.11%)	2 (11.11%)	14 (17.07%)	15 (17.05%)	9 (18.0%)	10 (19.2%)	5 (11.6%)
Asian		1 (5.56%)	1 (5.56%)			1 (2.0%)	1 (1.9%)	5 (11.6%)
Hispanic/Latino (Hispanic White)	1 (3.1%)	8 (44.44%)	8 (44.44%)	35 (42.68%)	36 (40.91%)	23 (46.0%)	24 (46.1%)	
American Indian/ Alaska Native				5 (6.10%)	7 (7.96%)	2 (4.0%)	2 (3.8%)	
Other/ Mixed Race	1 (3.1%)			3 (3.66%)	3 (3.51%)	4 (8.0%)	4 (7.7%)	1 (2.3%)

Continued:

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	INS-06-006	INS-08-008		INS-10-012		INS-12-015		INS-13-017
	Completed n=31 Enrolled n=32	Completed n=18	Enrolled n=18	Completed n=82	Enrolled n=88	Completed n=50	Enrolled n=52	Completed n=33 Enrolled n=43
Height (cm)								
Mean (SD)	67.6 (±3.3)	173.8 (11.3)	173.8 (11.3)	168.9 (10.0)	168.9 (9.8)	166.6 (9.6)	166.8 (9.7)	177.43 (6.559)
Median		175.8	175.8	171.0	171.0	167.5	167.5	178.00
Range		154.0 - 192.0	154.0 - 192.0	145.0 - 188.0	145.0 - 188.0	145.0-188.0	145.0-188.0	164.9-196.8
Weight (kg)								
Mean (SD)	162.8 (±25.0)	75.4 (14.5)	75.4 (14.5)	72.1 (10.6)	72.3 (10.6)	70.8 (10.1)	70.9 (10.1)	81.98 (10.042)
Median		73.8	73.8	73.0	73.3	69.6	69.6	81.60
Range		50.3 - 98.9	50.3 - 98.9	51.0 - 100.0	51.0 - 100.0	52.7-94.6	52.7-94.6	64.2-111.4

From NDA 205,525, Section Clinical Safety.

Study (INS-004-15-059) was submitted on January 7, 2016. Fifty-four (54) healthy adult subjects were exposed to dronabinol. Among them, 27 subjects were females and 27 males. Their ages were ranged from 23 to 49 years of age. Subjects' BMI ranged from 20.1 to 30.0 kg/m². Subjects' height and weight ranged from 148.0 to 199.0 cm and 60.1 to 112.9 kg, respectively.

8.2.3. Adequacy of the safety database:

Primary safety trial of Dronabinol Oral Solution was not conducted. The product is reviewed under the pathway of CFR 505(b)(2).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety review was primarily based on the 4 pharmacokinetic studies (INS-06-006, INS-08-008, INS-10-012, and INS-12-015) and one human abuse liability study (INS-13-017). After the NDA submission, the 5th PK (fed condition) study was submitted (1/7/2016). The data integrity and submission quality are acceptable.

8.3.2. Categorization of Adverse Events

The process of Applicant for recording, coding, and categorizing adverse events (AEs), as well as their approach to safety analysis is reasonable and appropriate.

- The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol.
- TEAEs were defined as related to the study drug during the corresponding treatment

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period.

- MedDRA Version 10.0 and Version 16.0 were used to code AEs.

8.3.3. Routine Clinical Tests

The following clinical laboratory tests were performed at screening, each check-in, and end-of-study:

- Physical examination
- Vital signs
- 12-lead ECG, blood pressure
- AE assessment
- Blood chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate transaminase, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total cholesterol, and total protein),
- Hematology (CBC with differential and platelets)
- Urinalysis
- Drug screen (ethanol, cocaine, THC, barbiturates, amphetamine, benzodiazepines, and opiates).

Medical Officer Comment:

The methodology and frequency of clinical testing were reasonable.

8.4. Safety Results

8.4.1. Deaths

There was no death in the five PK studies and one human abuse liability study of Dronabinol Oral Solution.

8.4.2. Nonfatal Serious Adverse Events

There were no non-fatal serious adverse events (SAEs) in the pharmacokinetic studies of Dronabinol Oral Solution. There was one non-fatal SAE (thinking abnormal occurring on the first day of drug administration with Dronabinol Oral Solution 10 mg) in the human abuse liability study. This SAE was determined to be serious because the subject was hospitalized for psychiatric assessment. The final conclusion suggested that the event was “an occurrence of a long-standing antisocial personality disorder which had not been previously diagnosed”.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

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Discontinuations occurred in the PK studies INS-06-006, INS-10-012 and INS-12-015, and in the human abuse trial INS-13-017 (Table 11); there was no discontinuation in Study INS-08-008.

Table 11: Patient Withdrawals and Explanations

	INS-06-006	INS-10-012	INS-12-015	INS-13-017
Investigator decision, due to adverse events not related to the study medication (torn neck muscle and foot fracture).	1			
Subject withdrew consent for personal reasons not further described		3	1	
Protocol non-compliance (positive urine alcohol screen).		1		

Continued:

	INS-06-006	INS-10-012	INS-12-015	INS-13-017
Protocol non-compliance (positive urine drug screen).		1		
Protocol non-compliance (positive urine pregnancy test).		1		
Protocol non-compliance (contraband found at search)			1	
Adverse event				3
Withdrawal by subject				3
Other				4

Note: From Section Summary of Clinical Safety, NDA 205,525;
 Other denotes that 4 subjects discontinued due to positive urine drug screens in Study INS-13-017.

In Study INS-004-15-059, one TEAE (vomiting) leading to treatment discontinuation occurred in Group C (Marinol Capsule, 5 mg under fasted conditions).

8.4.4. Significant Adverse Events

There was no new safety signal of Dronabinol Oral Solution identified as compared with the reference Marinol. Adverse events in the four pharmacokinetic studies were mostly mild and occasionally moderate in severity according to NCI-CTCAE; there were no severe events. In general, adverse events associated with Dronabinol Oral Solution were no more common or severe than those events associated with Marinol Capsules.

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The human abuse liability study used higher doses. No specific adverse events stand out as prominent in the human abuse study compared to the pharmacokinetic trials. Moderate anxiety was associated with Dronabinol Oral Solution 30 mg. The remainder of adverse events was mild.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The Integrated Summary of Safety (ISS) database included three Dronabinol Oral Solution trials (INS-08-008, INS-10-012, and INS-12-015). The clinical abuse liability study (INS-13-017) is not included, because the above-therapeutic doses were used. The Study INS-06-006 was also not included, because Dronabinol Syrup (an early formulation), instead Dronabinol Oral Solution, was used.

In the ISS database, 52 subjects received 4.25 mg Dronabinol Oral Solution, 86 received 5 mg Dronabinol Oral Solution, and 18 subjects received 10 mg Dronabinol Oral Solution. The comparators included 139 subjects who received 5 mg Marinol Capsules, and 18 subjects who received 10 mg Marion Capsules. The most commonly involved body systems were Nervous system disorders (i.e., dizziness, headache, paresthesia, somnolence), Gastrointestinal disorders (nausea, abdominal pain, diarrhea), and Psychiatric disorders (delusional perception, euphoric mood, anxiety, impaired concentration, clouded sensorium, insomnia) (Table 12).

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Table 12: Treatment-Emergent Adverse Events by Organ System

	INS-06-006	INS-08-008		INS-10-012 ^a	INS-12-015 ^a	Marinol® Capsules
	(Dronabinol Syrup)	(Dronabinol Oral Solution)	(Dronabinol Syrup)	(Dronabinol Oral Solution)	(Dronabinol Oral Solution)	
Cardiac disorders						
Palpitations					2	2
Eye disorders						
Blurry vision				1		
Gastrointestinal disorders						
Stomach discomfort	1					
Nausea	2	2		7	8	18
Paraesthesia oral	1					
Dry mouth			1			
Loose stool		1	1			
Abdominal pain				1	2	3
Diarrhea, multiple episodes				1		2
Diarrhea, single episode				1		
Dry mouth					1	2
Flatulence				1		
Vomiting, single episode				1		
General disorders and administration site conditions						
Malaise	1					
Fatigue		1		1		2
Chest tightness					1	1
Increased appetite					3	
Leg pain					1	
Pale skin color observed		1				1
Satiety				1		1
Infections and infestations						
Nasopharyngitis	1					
Viral pharyngitis	1					
Rhinitis		1				
Injury, poisoning and procedural complications						
Road traffic accident	1					
Lacerations on right hand			1			
Metabolism and nutrition disorders						
Anorexia				1	1	1
Hyperphagia				1		

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	INS-06-006 (Dronabinol Syrup)	INS-08-008		INS-10-012 ^a (Dronabinol Oral Solution)	INS-12-015 ^a (Dronabinol Oral Solution)	Marinol® Capsules
		(Dronabinol Oral Solution)	(Dronabinol Syrup)			
Nervous system disorders						
Headache	4	2	1	7	7	7
Dizziness	2	2		9	6	21
Clouded sensorium		1		3		2
Difficulty concentrating			1			
Giddiness			1			
Somnolence		1	4	3	7	11
Impaired concentration				2		
Dysgeusia					1	
Paresthasias					1	
Psychiatric disorders						
Delusional perception	1					
Euphoric mood, euphoria	1			1		
Clouded sensorium			1			
Anxiety				1		
Insomnia					2	2
Reproductive system and breast disorders						
Dysmenorrhoea	2					
Respiratory, thoracic and mediastinal disorders						
Epistaxis	2					
Pharyngolaryngeal pain	1					
Cough		1				
Itching in throat		1				
Nasal congestion						
Shallow breathing					1	2
Itching in throat		1				
Skin and subcutaneous tissue disorders						
Hyperhidrosis	1					
Ecchymosis						
Vascular disorders						
Feeling flushed		1				
Hot flashes				1		1
Hypotension, symptomatic hypotension				1		

^a The clinical study report presented numbers of subjects taking study medications as total treatments across the replicate dosing schedule. Exposure data here are provided as in the clinical study report (INS-10-012 and INS-12-015).

From Section of Clinical Safety, NDA 205,525

Notes: Drug exposures: IND-08-008 (Single dose): Dronabinol Oral Solution 10 mg (n=18), Dronabinol Oral Syrup 10 mg (n=18), Marinol Capsules 10 mg (n=18); IND-10-012 (Single dose): Dronabinol Oral Solution 5 mg (n=169), Marinol Capsules 5 mg (n=171); IND-12-015 (Single dose): Dronabinol Oral Solution 4.25 mg (n=52), Marinol Capsules 5 mg (n=52).

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In Study INS-004-15-059 (1/7/2016), there were no deaths and no serious adverse events (SAEs). Treatment-emergent adverse events (TEAEs) occurred in 9 (17%) subjects in Treatment A (Dronabinol Oral Solution 4.25 mg/0.85 mL under fed condition), 9 (17%) subjects in Treatment B (Marinol Capsule 5 mg, Fed), and in 12 (22%) subjects with administration of Treatment C (Marinol Capsule 5 mg, Fasted). One subject (Subject 0011073) in Treatment C was withdrawn from the study due to an AE (vomiting). The most commonly reported TEAE was headache; reported by 2 (3.8%) subjects in Treatment A, 1 (1.9%) subject in Treatment B, and 2 (3.8%) subjects in Treatment C. The second most commonly reported TEAE was euphoric mood: 2 (3.8%) subjects in Treatment A and 1 (1.9%) subject in Treatment C.

Table 13: Treatment-Emergent Adverse Events by Organ System in Human Abuse Liability Study INS-13-017

MedDRA System Organ Class Preferred Term	Placebo N=39 n (%)	Marinol® Capsules 10 mg N=35 n (%)	Marinol® Capsules 30 mg N=37 n (%)	Dronabinol Oral Solution 10 mg N=36 n (%)	Dronabinol Oral Solution 30 mg N=40 n (%)
Cardiac disorders					
Tachycardia	0	0	3 (8.1%)	0	1 (2.5%)
Palpitations	0	0	1 (2.7%)	0	1 (2.5%)
Ear and labyrinth disorders					
Hearing impaired	0	0	1 (2.7%)	0	0
Hyperacusis	0	1 (2.9%)	0	0	0
Eye disorders					
Asthenopia	1 (2.6%)	1 (2.9%)	3 (8.1%)	1 (2.8%)	3 (7.5%)
Photophobia	0	0	1 (2.7%)	1 (2.8%)	1 (2.5%)
Conjunctival hyperaemia	0	0	0	0	2 (5.0%)
Eye pain	0	0	2 (5.4%)	1 (2.8%)	0
Vision blurred	0	0	2 (5.4%)	0	1 (2.5%)
Eye irritation	0	0	0	0	1 (2.5%)
Dry eye	0	0	2 (5.4%)	0	0
Ocular hyperaemia	0	0	1 (2.7%)	0	0
Gastrointestinal disorders					
Dry mouth	1 (2.6%)	5 (14.3%)	16 (43.2%)	10 (27.8%)	16 (40.0%)
Paraesthesia oral	0	0	0	1 (2.8%)	0
Diarrhoea	1 (2.6%)	0	1 (2.7%)	0	0
Abdominal discomfort	0	0	1 (2.7%)	0	0
Gingival pain	0	1 (2.9%)	0	0	0
Food poisoning	1 (2.6%)	0	0	0	0
General disorders and administration site conditions					
Fatigue	1 (2.6%)	4 (11.4%)	13 (35.1%)	6 (16.7%)	12 (30.0%)
Feeling of relaxation	0	1 (2.9%)	1 (2.7%)	5 (13.9%)	2 (5.0%)
Hunger	1 (2.6%)	0	2 (5.4%)	2 (5.6%)	4 (10.0%)
Feeling hot	0	2 (5.7%)	0	0	2 (5.0%)
Thirst	0	0	0	0	2 (5.0%)
Chills	0	0	0	0	1 (2.5%)
Pain	0	1 (2.9%)	0	0	0
Infections and infestations					
Upper respiratory tract infection	0	1 (2.9%)	0	2 (5.6%)	1 (2.5%)
Hordeolum	0	0	0	0	1 (2.5%)
Pharyngitis	0	0	0	1 (2.8%)	0
Infectious colitis	0	0	1 (2.7%)	0	0

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MedDRA System Organ Class Preferred Term	Placebo N=39 n (%)	Marinol® Capsules 10 mg N=35 n (%)	Marinol® Capsules 30 mg N=37 n (%)	Dronabinol Oral Solution 10 mg N=36 n (%)	Dronabinol Oral Solution 30 mg N=40 n (%)
Injury, poisoning and procedural complications					
Soft tissue injury	1 (2.6%)	0	1 (2.7%)	0	0
Contusion	0	0	1 (2.7%)	0	0
Arthropod bite	1 (2.6%)	0	0	0	0
Investigations					
Alanine aminotransferase increased	0	0	0	1 (2.8%)	0
Aspartate aminotransferase increased	0	0	0	1 (2.8%)	0
Blood lactate dehydrogenase increased	0	0	0	1 (2.8%)	0
Gamma-glutamyltransferase increased	0	0	0	1 (2.8%)	0
Blood pressure increased	0	0	1 (2.7%)	0	0
Metabolism and nutrition disorders					
Increased appetite	0	1 (2.9%)	1 (2.7%)	1 (2.8%)	3 (7.5%)
Hyperphagia	0	2 (5.7%)	1 (2.7%)	1 (2.8%)	0
Polydipsia	0	0	1 (2.7%)	0	1 (2.5%)
Musculoskeletal and connective tissue disorders					
Sensation of heaviness	0	0	2 (5.4%)	0	2 (5.0%)
Muscle twitching	0	0	1 (2.7%)	1 (2.8%)	0
Muscle spasms	0	0	0	0	1 (2.5%)
Musculoskeletal stiffness	0	0	0	1 (2.8%)	0
Pain in extremity	0	0	0	1 (2.8%)	0
Neck pain	1 (2.6%)	1 (2.9%)	1 (2.7%)	0	0
Arthralgia	0	1 (2.9%)	0	0	0
Myalgia	0	1 (2.9%)	0	0	0
Nervous system disorders					
Somnolence	9 (23.1%)	10 (28.6%)	13 (35.1%)	11 (30.6%)	15 (37.5%)
Headache	1 (2.6%)	3 (8.6%)	2 (5.4%)	5 (13.9%)	4 (10.0%)
Dizziness	1 (2.6%)	2 (5.7%)	2 (5.4%)	1 (2.8%)	2 (5.0%)
Paraesthesia	0	0	3 (8.1%)	2 (5.6%)	1 (2.5%)
Dysgeusia	0	1 (2.9%)	0	0	2 (5.0%)
Disturbance in attention	0	0	0	2 (5.6%)	0
Hypoaesthesia	0	1 (2.9%)	0	0	1 (2.5%)
Hypotonia	0	0	0	0	1 (2.5%)

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8.4.6. Laboratory Findings

Clinical laboratories were evaluated for each of the Dronabinol Oral Solution pharmacokinetic studies and for the human abuse liability study. No clinically significant abnormalities were identified, and no group trends were detected.

8.4.7. Vital Signs

Vital signs were monitored and physical examination was conducted during each of the dronabinol pharmacokinetic studies. No clinically significant abnormalities were identified, and no group trends were detected. In the human abuse liability study, there were no marked changes from baseline vital sign measurements during the treatment phase and most results were within normal limits. Four subjects showed clinically important but transient elevations of pulse rate or blood pressure.

8.4.8. Electrocardiograms (ECGs)

ECG evaluations in the pharmacokinetic studies had no significant findings. The human abuse liability study was conducted in recreational cannabinoid drug users, no clinically significant abnormalities were identified at either screening or during the treatment phase. Summary of ECG parameter results were found to be comparable between screening, each admission, and the follow-up visit.

8.4.9. QT

Upon DGIEP request, the Division of Cardiovascular and Renal Products (DCRP) QT Interdisciplinary Review Team (QT-IRT) assessed the QT effect of dronabinol reported by Sellers et al (Sellers, 2013). The QT-IRT concluded that the results of the Sellers study were unable to support the safety of Dronabinol Oral Solution, and suggesting that an independent QT study of the product at the upper limit of the antiemetic dosing range was required. Since the time the reference product was approved, cardiac related events including syncope and potential QT prolongation were under review by the Office of Surveillance and Epidemiology in order to determine if there is a causal link. To date, the causal relationship between Marinol (dronabinol) treatment and cardiac adverse events has not been identified by OSE review.

8.4.10. Immunogenicity

No assessment of immunogenicity for Dronabinol Oral Solution was performed.

8.5. Analysis of Submission-Specific Safety Issues

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Potential safety issues of drug class effect, non-clinical signal, or uncertainty about novel moiety were not found.

8.6. Specific Safety Studies/Clinical Trials

No specific study was conducted to evaluate a specific safety concern.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

No potential issues related to human carcinogenicity or tumor development were identified.

8.7.2. Human Reproduction and Pregnancy

Human reproduction and pregnancy were not evaluated during the development program.

8.7.3. Pediatrics and Assessment of Effects on Growth

Dronabinol is indicated for treatment of anorexia associated with weight loss in patients with AIDS. The number of children age 0 to 14 years old with AIDS is very small: (1) Approximately 750 patients age less than 13 years have AIDS and develop anorexia in the U.S.; and (2) approximately 120 patients age 13 to 14 have AIDS and develop anorexia in the U.S. Thus, the PeRC review granted a waiver of studying anorexia in AIDS patient age less than 14 years old.

Deferral is requested by the Applicant for all age groups (except the group for waiver) as follows:

- 15-17 years: (b) (4) trial in pediatric AIDS patients.
- 0-17 years: A phase 2, multiple-dose, dose ranging, PK/PD trial in pediatric cancer patients.
- 0-17 years: Pivotal multiple-dose tolerability, and efficacy study in pediatric cancer patients.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Controlled Substance Staff (CSS) was consulted that the Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, and

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presents a higher risk of unintentional overdoses, if abused. Accordingly, they recommend placing Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970).

Drug abuse potential of Dronabinol Oral Solution was studied by the Applicant and compared with the reference Marinol Capsules (Study INS-13-017). The study concluded that Dronabinol Oral Solution had abuse potential comparable to that of Marinol Capsules in recreational cannabis users. No statistically significant or clinically relevant differences were observed between the comparable doses of Marinol Capsules and Dronabinol Oral Solution on any of the study endpoints.

Drug overdose, withdrawal, and rebound experiences were not studied.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The relevant postmarketing safety issues of Marinol were searched and reviewed by the Safety Evaluator of DDRE (Division of Drug Risk Evaluation) Ann Corken Mackey, R.Ph (3/22/2006). The search used the Adverse Event Reporting System (AERS) between the approval of drug (May 1985) and February 9, 2006. A total of 27 cases were available for review in the document. A brief summary of her findings is provided as follows:

There was one fatality that was possibly due to dronabinol use. This case involved an 88-year-old male who was participating in a study to test the use of dronabinol to treat agitation associated with Alzheimer's disease (patient received 10 mg of dronabinol a day for 36 days). He fell and experienced a fatal intracerebral hemorrhage.

Half of the adverse events identified were neurologic or psychiatric in nature. Of the 7 neurologic adverse events, 6 cases involved seizure and 1 involved stupor (2 patients were hospitalized and 1 case was described as life threatening). Most patients' seizures were likely associated with an underlying seizure history or recent stroke history (two cases provided insufficient information to make a determination [one of these patients had underlying Alzheimer's disease]). Psychiatric events included altered mental status, confusion, delirium, hallucinations, and "homicidal" behavior; 7 patients were hospitalized and 1 case was reported as life threatening. Most of the cases reporting psychiatric events provided little information (e.g., details of event, medical history not reported). With the exception of seizure, the neurologic and psychological adverse events are labeled.

Three cases of misuse/overdose were identified in this case series. One case involved an unintended overdose (patient mixed up his medications and took a one-time overdose of

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dronabinol) and two cases involved intentional misuse/overdose (one patient was reported to have a history of drug abuse). All 3 patients experienced neuro-psych events (e.g., "passed out," delusions, agitation, depressed level of consciousness, nightmares); in addition, one patient experienced an allergic-type reaction. The patient reporter who mixed up his medications stated that he continued to "black out occasionally;" it appeared that the patient who had a history of substance abuse recovered and the outcome for third patient was not provided. The abuse potential is addressed in the label for dronabinol.

Three cases of constipation/intestinal obstruction were reported; all patients recovered when the drug was discontinued. These patients had medical history of conditions associated with constipation (i.e., multiple sclerosis, constipation disorder) or were receiving concomitant medications known to cause constipation (e.g., narcotics).

Out of 27 cases identified in this case series, 3 patients who took dronabinol experienced falls/fractures, including 1 fatality. The 3 patients ranged in age from 88 to 92 years of age. Although most patients had confounding factors (Alzheimer's disease/dementia, history of syncope, narcotic use, advanced age), a role of Dronabinol (with labeled adverse events of dizziness and hypotension) could not be ruled out.

A meta-analysis reported 30 randomized studies comparing cannabinoids (i.e., oral nabilone n=16, oral dronabinol n=13, and injectable levonantradol n=1) with placebo or other antiemetics (e.g., prochlorperazine [most common comparator], metoclopramide, chlorpromazine) for control of chemotherapy-induced nausea and vomiting (total of 1366 patients). Side effects occurred significantly more often with cannabinoids. Those reported included feeling "high," sedation or drowsiness, euphoria, dizziness, dysphoria or depression, hallucinations, paranoia, and arterial hypotension. Patients given cannabinoids were more likely to withdraw from studies due to side effects. The authors concluded that cannabinoids may be useful as mood adjuvants for controlling chemotherapy-related sickness, but that potentially serious adverse events are likely to limit their widespread use.

The reviewer suggested the Division to revise the label to include 1) a warning about use of this drug in elderly, with an emphasis on recommending a lower starting dose, and 2) that seizure has been reported in patients who had underlying history of seizure; however, the role of dronabinol could not be ruled out (note that seizure is a labeled event for the cannabinoid nabilone).

Medical Officer Comment:

The above DDRE recommendations had been incorporated into the revised version of Marinol label.

8.8.2. Expectations on Safety in the Postmarket Setting

See Section 8.8.1, there is no additional expectation on safety in the postmarket setting.

8.9. Additional Safety Issues From Other Disciplines

The clinical significance of prolonged stay of the product in oral cavity has not been studied. Dronabinol Oral Solution should be swallowed instantly, because prolonged stay in oral cavity may lead to the diffusion of drug into the blood through tissues under the tongue. The pharmacokinetics differs between administration *per os* and sublingual. The former will go through the GI tract and the First Pass effect will only allow approximately 20% of the administered dose to reach the target sites, whereas the latter directly enters systemic blood circulation and reaches the target sites with full potency.

8.10. Integrated Assessment of Safety

The adverse event profile of Dronabinol Oral Solution 4.25 mg in the crossover pharmacokinetic trials included diarrhea, nausea, dizziness, headache and somnolence.

These adverse events were similar to that of Marinol Capsules 5 mg. No new safety signals specific for the oral solution were identified.

The Controlled Substance Staff (CSS) concluded that the Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, and presents a higher risk of unintentional overdoses, if abused. Accordingly, they recommend placing Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970).

9 Advisory Committee Meeting and Other External Consultation

No advisory committee meeting or other external consultations was held.

10 Labeling Recommendations

Dronabinol Oral Solution labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS was not recommended.

12 Postmarketing Requirements and Commitments

The proposed PMR studies were outlined as follows:

Nonclinical Studies:

Title: "Three-month repeat dose toxicity and toxicokinetic study with Dronabinol Oral Solution in juvenile rats with a 28-day recovery period"

This will be a 3-month repeat-dose (b) (4) juvenile rat toxicology study of Delta-9-Tetrahydrocannabinol (THC), followed by a 28-day recovery period. Prior to conducting this three-month study, a 28-day, daily, repeat-dose, oral gavage dose-range finding study will be conducted to select appropriate doses. A draft copy of the three-month study protocol was submitted on April 1, 2015 (serial #0055).

Clinical Studies:

1)

2)

(b) (4)

3)

(b) (4)

13 Appendices

13.1. References

Bedi G, Foltin RW, Gunderson EW, Rabkin J, Hart CL, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology (Berl)*. 2010, 212:675-686.

DeJesus E, Rodwick BM, Bowers D, Cohen CJ, and Pearce D. Use of dronabinol improves appetite and reverses weight loss in HIV/AIDS-infected patients. *J Int Assoc Physicians AIDS care* 2007, 6:95-100. DOI: 10.1177/1545109707300157.

Haney M, Gunderson EW, Rabkin J, Hart CL, Vosburg SK, et al. Dronabinol and marijuana in HIV-positive marijuana smokers. *J Acquir Immune Defic Syndr*. 2007, 45:545-554.

Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. 2007, 23:533-543.

Sellers EM, Schoedel K, Bartlett C, Romach M, Russo EB et al. A multiple-dose, randomized, double blind, placebo controlled, parallel group QT/QTc study to evaluate the electrophysiologic effects of THC/CBD spray. *Clin Pharm Drug Devel* 2013; 2:285-294.

Slatkin NE. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: Beyond prevention of acute emesis. 2007 [www.Supportive Oncology.net](http://www.SupportiveOncology.net)

Thompson LA, and O'Bryant CL. Chemotherapy-induced nausea and vomiting: Guideline summary and clinical challenges. *Pharmacy Practice News*. 2013; Clinical:19-23.

Wheeler DA. Weight loss and disease progression in HIV infection. *AIDS Reader*. 1999;9:347-353.

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13.2. Financial Disclosure

The following table presents the financial disclosure information. The Applicant has adequately disclosed the information as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Covered Clinical Studies: INS (06-006, 08-008, 10-012, 12-015, and 13-017)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant) N/A
Total number of investigators identified: <u>54</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>None</u> Significant payments of other sorts: <u>None</u> Proprietary interest in the product tested held by investigator: <u>None</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>None</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes N/A	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes N/A	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>54</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant) N/A

13.3. Individual Studies Used in Safety Evaluation

1) Study INS-13-017

Study Title: A Single-Dose, Double-Blind, Double-Dummy, Randomized, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Dronabinol Oral Solution in Recreational Cannabinoid Users.

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

Study Design: This was a single-dose, randomized, double-blind, placebo and active-controlled, 5-way crossover study. Each subject participated in a medical screening phase (a qualification phase of drug discrimination) and a treatment phase that consisted of 5 Treatment periods.

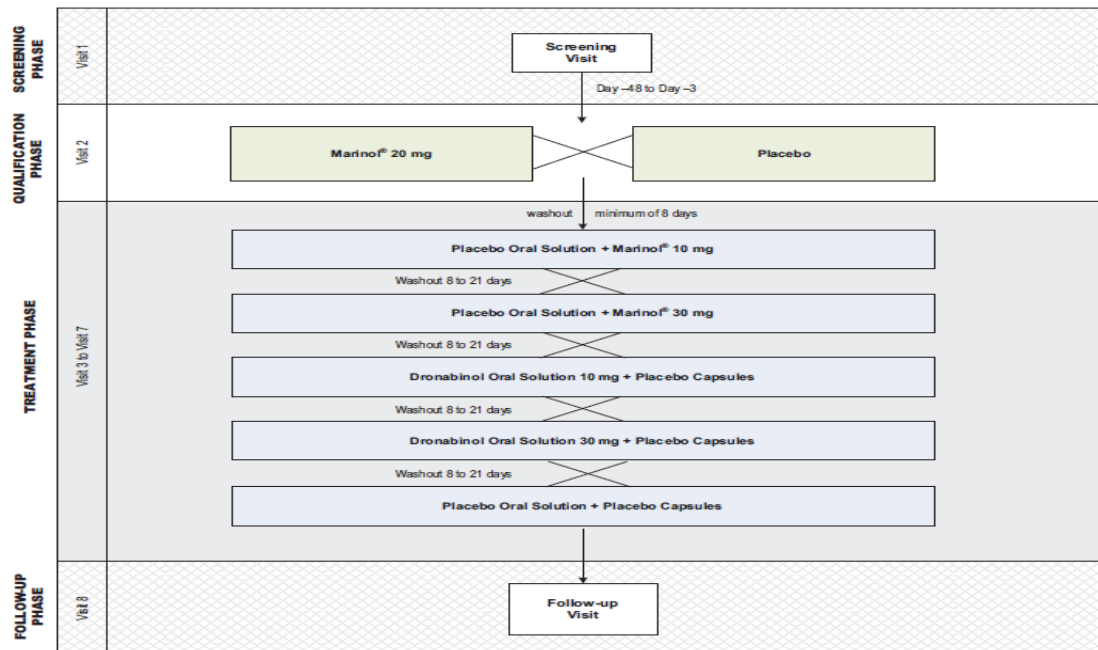
In the Qualification phase, subjects received 20 mg Marinol Capsules and placebo in a randomized crossover manner. The Qualification phase involved a 5-night (6-day) inpatient stay in the research clinic. Subjects were dosed with 20 mg Marinol or placebo on Days 1 and 3. Each dose was separated by at least 48 hours washout period. Subjects were discharged on Day 4. Eligible subjects were then enrolled in the Treatment phase, which consisted of five 3-night (4-day) inpatient stays in the research clinic. 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:

- Placebo oral solution + 10 mg Marinol
- Placebo oral solution + 30 mg Marinol
- 10 mg Dronabinol Oral Solution + Marinol placebo
- 30 mg Dronabinol Oral Solution + Marinol placebo
- Placebo oral solution + Marinol placebo

The study design is summarized in Figure 1.

Figure 1 (INS 13-017): Study Schematic

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From Study Report of INS-13-017.

Primary Pharmacodynamic Endpoint:

The primary PD endpoint was Emax on Drug Liking VAS (visual analog scale). It is a 25-point difference in Drug Liking VAS Emax between 20 mg dronabinol and placebo.

Safety Endpoints:

The following safety endpoints were evaluated:

- Incidence, frequency and severity of AEs
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Vital signs (heart rate, sitting BP, respiratory rate, oral temperature)
- Physical examination results
- 12-lead ECG

Major Inclusion Criteria:

1. Healthy male or female subjects 18 to 55 years of age
2. Body mass index (BMI) within the range of 18 to 33 kg/m², inclusive, and a minimum weight of 50 kg
3. Current recreational cannabinoid users who had used cannabinoids

Major Exclusion Criteria:

1. Substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years

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2. Clinically significant abnormalities on physical examination, medical history, 12-lead electrocardiogram (ECG), vital signs, or laboratory values, as judged by the investigator or designee
3. History or presence of any clinically significant illness (e.g., cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, musculoskeletal, or psychiatric) or any condition which, in the opinion of the investigator, would have jeopardized the safety of the subject or the validity of the study results
4. History of syncope within 3 months prior to Screening or any history of recurrent and/or unexplained episodes of syncope
5. Any history of epilepsy or seizures (except childhood febrile seizures)
6. History of cardiac disorder within 3 months prior to Screening

Schedule of Pharmacodynamic and Safety Assessments:

The PD and safety variables assessed and laboratory tests conducted throughout the study are summarized in the following table. Efficacy was not examined in the present study.

Table 1 (INS 13-017): 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	X	pre	0.5	1	2	3	4	6	8	24	X
Oral Temperature	X	X	X	pre									X
12-Lead ECG	X	X					X						X

^a Focusing on any changes since the last visit

^b Symptom-directed physical examination performed at the investigator's discretion

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(Continued)

Assessment	Screening		Qualification						Treatment Period 1 to Treatment Period 5						Follow-up												
	1		2						3 to 7						8												
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)																		
Urine Drug Screen	X	X							X																		
Breath Alcohol	X	X							X																		
Clinical Laboratory	X								X						X												
Concomitant Medications		X	X	<	-	-	-	-	-	-	-	-	-	-	>	X											
AE Monitoring ^c		X	X	pre	0.5	1	2	3	4	6	8	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	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	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.
^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

Statistical Populations:

- Safety population: All randomized subjects who received any study treatment in the treatment phase (43 subjects)
- PD population: All randomized subjects who completed all treatment sessions and had no major protocol deviations that would have excluded them from analysis (33 subjects)
- Three subjects (7.0%) discontinued due to treatment-emergent adverse events (TEAEs): 2 subjects after receiving 30 mg Marinol, 1 subject discontinued after receiving 30 mg Dronabinol Oral Solution.

Subjects were primarily male (86.0%) and white (74.4%) with a mean age of 36 years (from 21 to 55 years). African American and Asian each accounted for 11.6%. The mean BMI was 26 kg/m².

Table 2 (INS 13-017): Demographic and Baseline Characteristics

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Characteristic	Safety Population N=43
Age (years)*	
Mean (SD)	36.0 (8.84)
Min, Max	21, 55
Sex, n (%)	
Male	37 (86.0%)
Female	6 (14.0%)
Race, n (%)	
White	32 (74.4%)
Black or African American	5 (11.6%)
Asian	5 (11.6%)
Other	1 (2.3%)
BMI (kg/m ²)	
Mean (SD)	26.0 (2.53)
Min, Max	20.9, 31.9

Source: Table 14.1.4

BMI=body mass index; SD=standard deviation

*Age at informed consent.

Percentage is calculated based on the number of subjects in the Safety Population as the denominator.

Recreational Drug Use History:

All subjects had previous experience with cannabinoids. Previous use of opioids or morphine derivatives was common (74%). Previous uses of hallucinogens, depressants and dissociative anesthetics were less common (18.6%, 14.0%, and 9.3%).

Pharmacodynamic Results of the Qualification Phase:

- All subjects in PD Population met the PD Qualification criteria.
- The subjects' Drug Liking VAS Emax values for 20 mg Marino were ≥ 60 (range: 75 to 100) and showed differences of at least 15 points greater than placebo.
- All subjects showed placebo responses ranged from 40 to 60.
- Overall, the mean and median placebo Emax values at the neutral point (50.5 and 50.0, respectively); and
- High Emax with Marinol (95.5 and 100.0, respectively) suggest the test population was sensitive and appropriate for the study.

Table 3 (INS 13-017): 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: Table 14.2.1

E_{max}=maximum effect; PD=pharmacodynamic; range=minimum, maximum; SD=standard deviation; VAS=visual analog scale

Pharmacodynamic Results of the Treatment Phase:

- As shown in Table 4, placebo Drug Liking VAS E_{max} values (primary endpoint) were close to neutral (50); the values higher with 10 mg Marinol and 10 mg Dronabinol Oral Solution, and the highest with the 30 mg doses of Marinol and Dronabinol Oral Solution.
- Median T_{E_{max}} (time to peak effect) was 0.5 hours with placebo and ranged from approximately 2 to 3 hours with Marinol and 1.5 to 2 hours with Dronabinol Oral Solution.
- Minimal effects were observed on Drug Liking VAS E_{min}; the values were close to neutral for the placebo and active treatments (median of 50.0 for all treatments).
- Compared to E_{max}, active treatment-related effects on Drug Liking VAS TA_AUE (time-averaged area under the effects curve) were less pronounced relative to the placebo; however, the pattern of results was similar to E_{max}, with similar effects between comparable doses of Marinol and Dronabinol Oral Solution.

Table 4 (INS 13-017): PD Parameters for Drug Liking VAS (PD Population)

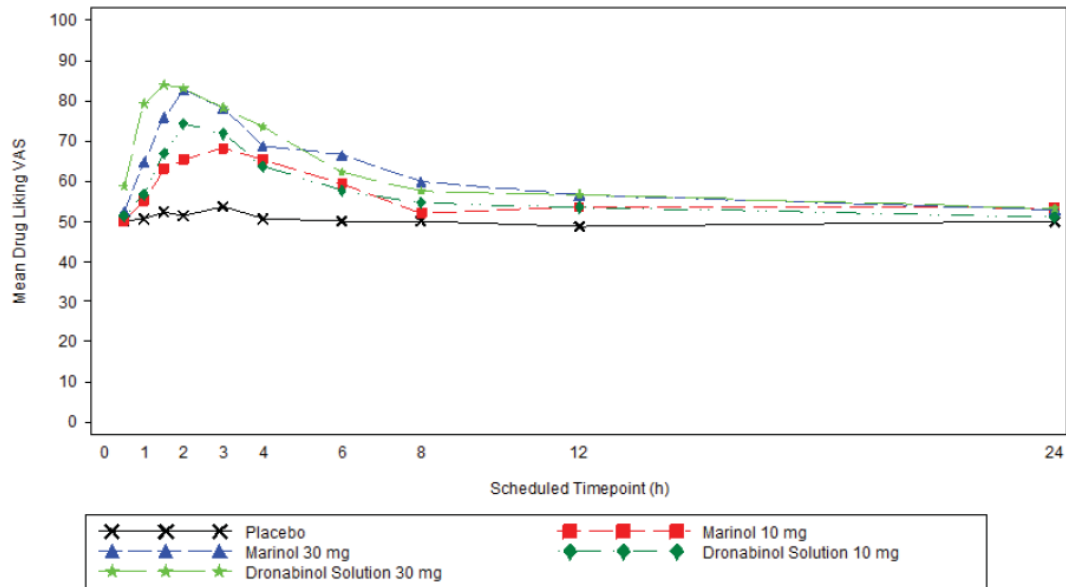
Endpoint/Statistic		Marinol [®]			Dronabinol Oral Solution	
		Placebo (N=33)	10 mg (N=33)	30 mg (N=33)	10 mg (N=33)	30 mg (N=33)
E _{max}	Mean (SD)	54.2 (10.12)	78.1 (19.08)	89.0 (13.30)	81.4 (16.18)	91.7 (11.51)
	Median	51.0	75.0	96.0	83.0	100.0
T _{E_{max}} (h)	Median	0.500	2.983	2.000	2.000	1.500
	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
T _{E_{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: Table 14.2.2.1.2

E_{max}=maximum effect; E_{min}=minimum effect; h=hour; N=number of subjects; PD=pharmacodynamic; range=minimum, maximum; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; T_{E_{max/min}}=time to peak effect; VAS=visual analog scale

The mean scores over time for Drug Liking VAS are shown in Figure 2. The mean placebo scores remained near neutral for the duration of the study, responses to 10 mg of Dronabinol Oral Solution and Marinol were higher and showed peak effects between 2 to 3 hours post-dose and a return to neutral by 8 hours post-dose. The higher dose (30 mg) of both Dronabinol Oral Solution and Marinol showed higher and slightly earlier peak effects (1.5 and 2 hours, respectively), as well as a slightly longer duration (e.g., up to 12 hours post-dose).

Figure 2 (INS 13-017): Mean Drug Liking VAS Scores over Time (PD Population)



Source: Figure 14.2.2.1.1

PD=pharmacodynamic; VAS=visual analog scale

Responses range from 0 (Strong disliking) to 100 (Strong liking) with neutral point 50 (Neither like nor dislike).

Pharmacodynamic Conclusions by Applicant:

PD analysis was consistent across all subjective measures and demonstrated the following:

- The Applicant stated that 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 to 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.

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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.

Medical Officer Comments:

The clinical reviewer concludes that the sweetened alcohol vehicle may result in a higher abuse potential as compared with the sesame oil vehicle, and therefore, agrees with the CSS conclusion that Dronabinol oral solution has a greater potential for abuse than the Marinol capsules, and other drugs in Schedule III, which presents a higher risk of unintentional overdoses, if abused. It is reasonable to place Dronabinol oral solution in Schedule II of the CSA (the Controlled Substances Act of 1970).

Safety Evaluation:

Test Product: Dronabinol Oral Solution; Dose: 10 mg, 30 mg, oral administration

Reference Products: Marinol Capsules 10 mg, 30 mg

Extent of Exposure: Forty-three subjects were randomized to the Treatment phase received a single dose of Marinol (10 mg and 30 mg), and Dronabinol Oral Solution (10 mg and 30 mg) in 5 separate Treatment periods.

Safety Findings: One serious AE (thinking abnormal in a subject from the Dronabinol Oral Solution 10 mg group, resolved) was reported. A total of 154 subject-exposures with AEs were reported during the treatment phase of the study.

Table 5 (INS 13-017): Adverse Events by Treatment Group

	Dronabinol Oral Solution		Marinol [®] Capsules		Placebo
	10 mg	30 mg	10 mg	30 mg	
Number of Subjects who received Study Medication During the Treatment Phase	36	40	35	37	39
Total Number of Subjects with Treatment Emergent Adverse Events	33 (91.7)	39 (97.5)	30 (85.7)	35 (94.6)	17 (43.6)

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	Dronabinol Oral Solution		Marinol [®] Capsules		Placebo
	10 mg	30 mg	10 mg	30 mg	
Total Number of Serious Adverse Events	1 (2.8)	0	0	0	0
Discontinued Due to an Adverse Event	0	1 (2.5)	0	2 (5.4)	0
Any severe adverse event	1 (2.8)	0	0	0	0
Any adverse event related to study drug	33 (91.7)	39 (97.5)	29 (82.9)	35 (94.6)	14 (35.9)

From Summary of Clinical Safety, NDA 205525

The most common treatment-emergent adverse events (TEAE) were euphoric mood for Dronabinol Oral Solution 30 mg (87.5%), Marinol Capsules 30 mg (81.1%), Dronabinol Oral Solution 10 mg (72.2%), and Marinol Capsules 10 mg (68.6%). The highest incidence of potentially abuse-related events observed for Marinol Capsules and Dronabinol Oral Solution were related to euphoric mood, somnolence, and feelings of relaxation. The incidence of TEAEs was comparable between the treatments administered at the same dose level (Marinol Capsules 10 mg vs. Dronabinol Oral Solution 10 mg and Marinol Capsules 30 mg vs. Dronabinol Oral Solution 30 mg). Across treatments, the majority of TEAEs was mild in severity and considered to be related to the study treatment.

There were no marked changes from baseline to follow-up for any clinical laboratory test parameters or vital sign measurements. Summary ECG results were comparable between each admission during the treatment phase and at follow-up. Few clinically significant abnormal vital sign and ECG results were observed, and all were transient. Overall, the treatments administered in this study were well tolerated in recreational cannabinoid drug users.

Recommendations by Controlled Substance Staff (2/26/2016):

1. Although the human abuse potential study conducted by Sponsor demonstrates that the Dronabinol Oral Solution has an abuse potential comparable to that of Marinol in recreational cannabis users when taken in single doses (no greater than 30 mg), as prescribed, the in vitro study data demonstrate that the formulations differ in their physicochemical properties, which affects how and the extent to which the drug can be abused. The Dronabinol Oral Solution can be manipulated to afford highly concentrated dronabinol extracts that can be reconstituted for smoking using vaporizers such as electronic cigarettes (e-cigs) or the Volcano vaporizer. Although the intravenous abuse of dronabinol is not a common route of abuse, the concentrated extracts of dronabinol in solvents that can be easily evaporated afford residues that could be reconstituted for intravenous abuse. When considering the oral route of abuse, Dronabinol Oral Solution serves as an accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) that can be easily abused orally.

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2. Dronabinol Oral Solution has a greater potential for abuse than Marinol capsules and presents a higher risk of unintentional overdose, if abused. Accordingly, a recommendation to place Dronabinol Oral Solution in Schedule II of the Controlled Substance Act will follow.
3. Regarding labeling of Dronabinol Oral Solution, CSS recommends the inclusion of a warning indicating that high drug content in the dispensed product adds to the risk of adverse outcomes from abuse and misuse of the formulation.

Medical Officer Comment:

The recommendation of Controlled Substance Staff will be incorporated in the label of Dronabinol Oral Solution.

2) Study INS-06-006

Title of Study: A Single Site, Randomized, Ascending Dose Study to Determine the Pharmacokinetics, Safety and Tolerability of Dronabinol Syrup in Healthy Volunteers under Fasted Conditions

Study Design: This study was a Phase 1, single center, randomized, single-blind, placebocontrolled, sequential ascending dose, 4- sequence study under fasting conditions. In brief, 31 of the 32 enrolled subjects completed the 5 periods studies. In each study period, subjects received three of four doses of Dronabinol Syrup and one dose of placebo. The treatments were after an overnight fast, and a seven-day washout interval between treatments.

Study Centers: PRACS Institute, Ltd., 4801 Amber Valley Parkway, Fargo, ND 58104

Test Product: Dronabinol Oral Syrup 5 mg/mL

Dose = 2.5 mg, 2.5 mg with 240 mL water, 5 mg, 10 mg, oral administration

Reference Product: Placebo

Duration of Treatment: Four single dose treatments were administered with a 7-day washout period between doses

Safety Findings: No serious adverse events (SAEs) were reported over the course of this study. Thirteen (13) subjects experienced a total of 22 AEs over the course of the study; and 2 subjects who had adverse events at two different treatment periods (Row 3 of Table 1). The AEs were mild to moderate in severity; and the numbers of subjects and AEs are presented in Table 1.

Table 1 (INS-06-006): Adverse Events by Period and Treatment Group

	Dronabinol Syrup 2.5 mg	Dronabinol Syrup 2.5 mg with 240 mL water	Dronabinol Syrup 5 mg	Dronabinol Syrup 10 mg	Placebo
Number of Subjects who received study medication	24	24	23	23	31
Total Number of Subjects with Adverse Events	4	1	3	6	1
Total Number of Adverse Events	5	1	6	9	1
Number of Possibly Related Adverse Events	5	1	6	9	1

From Summary of Clinical Safety, NDA 205525

Adverse events occurred less frequently with Dronabinol Syrup 2.5 mg taken with water than the other dronabinol syrup test formulations. The general profile of adverse event frequencies was similar between formulations. The most commonly reported AEs were dizziness and headache. Other than two reports of moderate severity events (one report of nausea and one report of traffic accident, each potentially related to dronabinol), all other events were of mild severity.

Safety Conclusion: There was no clinically significant adverse event. Dronabinol was well tolerated as a 2.5 mg dose (0.5 mL of 5 mL syrup), 2.5 mg dose (0.5 mL of 5 mg/mL syrup) with 240 mL water, 5 mg dose (1 mL of 5 mg/mL syrup), or 10 mg dose (2 mL of 5 mg/mL syrup) administered to healthy adult subjects under fasting conditions.

3) Study INS-08-008

Title of Study: 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: This was a Phase 1, single-dose, three-period, three-sequence crossover study with a 7-day washout between study periods.

Study Centers: CEDRA Clinical Research, LLC, 8501 North MoPac Expressway, Suite 200, Austin, Texas 78759

Test Products: Dronabinol Oral Syrup 5 mg/mL (Treatment A), Dronabinol Oral Solution 5 mg/mL (Treatment B), and Marinol Capsules 10 mg (Treatment C)

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Reference Product: Marinol® Capsules 10 mg, 1x10 mg capsule

Duration of Treatment: Three single dose treatments were administered with a 7-day washout period between doses

Safety Findings: No serious adverse events (SAEs) were reported over the course of this study. Eleven (11) of 18 enrolled subjects experienced a total of 35 adverse events (AEs) over the course of the study, and at least one subject had multiple AEs at more than one treatment period (Row 3 of Table 1). Adverse events were mild to moderate in severity. Thirty-one of the adverse events were possibly or probably related to study treatment; 4 events were not related. The numbers of adverse events by treatment group are summarized below.

Table 1 (INS-08-008): Adverse Events by Period and Treatment Group

	Dronabinol Oral Syrup, 10 mg (Treatment A)	Dronabinol Oral Solution, 10 mg (Treatment B)	Marinol® Capsules 10 mg (Treatment C)
Number of Subjects who received study medication	18	18	18
Total Number of Subjects with Adverse Events	8	7	6
Total Number of Adverse Events	11	14	10

From Summary of Clinical Safety, NDA 205525

The most commonly reported AEs were somnolence (n=9; 4 following Dronabinol Oral Syrup, 1 following Dronabinol Oral Solution, and 4 following Marinol Capsules), headache (n=4; 1 following Dronabinol Oral Syrup, 2 following Dronabinol Oral Solution, and 1 following Marinol Capsules), and dizziness (n=4; 2 following Dronabinol Oral Solution and 2 following Marinol Capsules).

Safety Conclusion: There was no clinical significant adverse event. Dronabinol was well tolerated as a 10 mg oral syrup dose or oral solution dose when administered to healthy adult subjects under fasting conditions.

4) Study INS-10-012

Title of Study: Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 5 mg versus Marinol Capsules 5 mg Under Fasted Conditions

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Study Design: This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate design crossover study with a 7-day washout between study periods.

Study Centers: Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services (WCTCRS), 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217

Test Products: Dronabinol Oral Solution 5 mg/mL Marinol Capsules 5 mg
Dose = Dronabinol Oral Solution 5 mg/mL (1 x 1 mL) (Treatment A, n=169), Marinol Capsules 5 mg (1 capsule) (Treatment B, n=171)

Duration of Treatment: Four single dose treatments were administered with a 7-day washout period between doses

Safety Findings: No deaths and no serious adverse events (SAEs) were reported in both groups over the course of this study. A total of 45 AEs were reported in the Treatment A group, and 47 AEs in the Treatment B group. Adverse events were mild to moderate in severity in both groups. The most common AEs were clouded sensorium, dizziness, headache, nausea, and somnolence in both groups. The numbers of adverse events by treatment group are summarized below.

Table 1 (INS-10-012): Adverse Events by Treatment Group

	Dronabinol Oral Solution, 5 mg	Marinol[®] Capsule, 5 mg
Number of Subjects who received Study Medication (Total number of study medication treatments during the replicate crossover design) ^a	169	171
Total Number of Subjects with Adverse Events	26	24
Total Number of Adverse Events	45	47

^a The clinical study report presented numbers of subjects taking study medications in the Safety Data Tables and Figures, Table 14.3, as total treatments across the replicate dosing schedule. Exposure data here are provided as in the clinical study report (INS-10-012 and INS-12-015). Note that numbers of subjects taking Dronabinol Oral Solution and Marinol[®] Capsules are presented differently in the ISS, as 86 subjects each taking two doses of Dronabinol Oral Solution and as 87 subjects each taking two doses of Marinol[®] Capsules.

Safety Conclusion: There were no clinically significant adverse events or clinical laboratory tests related to the study medication.

5) Study INS-12-015

Title of Study: A Single-Dose Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 4.25 mg versus Marinol Capsules 5 mg under Fasted Conditions

Clinical Review
Wen-Yi Gao, MD, PhD
NDA 205,525/000
Syndros (Dronabinol Oral Solution)

Study Design: This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate design crossover study with a 7-day washout between study periods. Fifty-two (52) subjects were enrolled to receive four separate single doses of Dronabinol Oral Solution or Marinol capsules in four study periods following overnight fasting.

Study Centers: Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services (WCTCRS), 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217

Test Products: Dronabinol Oral Solution 4.25 mg/0.85 mL
Marinol Capsules 5 mg
Dose = Dronabinol Oral Solution 4.25 mg (1 x 4.25 mg/0.85 mL) with 240 mL water, Marinol Capsules 5 mg (1 capsule)

Duration of Treatment: Four single dose treatments were administered with a 7-day washout period between doses

Safety Findings: No deaths, no serious adverse events (SAEs) were reported from both treatment groups over the course of this study. A total of 90 adverse events (AE) were reported by 25 subjects from the 52 subjects enrolled; and 44 AEs were reported following Dronabinol Oral Solution 4.25 mg/mL and 46 following Marinol Capsules 5 mg (Table 1). All of the 90 AEs were mild or moderate. The most commonly reported AEs were nausea (n = 14; 8 following Dronabinol Oral Solution 4.25 mg/mL and 6 following Marinol Capsules 5 mg); dizziness (n = 13; 6 following Dronabinol Oral Solution 4.25 mg/mL and 7 following Marinol Capsules 5 mg); somnolence (n = 12; 7 following Dronabinol Oral Solution 4.25 mg/mL and 5 following Marinol Capsules 5 mg); and headache (n = 11; 7 following Dronabinol Oral Solution 4.25 mg/mL and 4 following Marinol Capsules 5 mg).

Table 1 (INS-12-015): Adverse Events by Treatment Group

	Dronabinol Oral Solution, 4.25 mg /0.85 mL	Marinol[®] Capsules, 5 mg
Number of Subjects who received Study Medication (Total number of study medication treatments during the replicate crossover design)	101	102
Total Number of Subjects with Adverse Events	18	18
Total Number of Adverse Events	44	46

^a The clinical study report presented numbers of subjects taking study medications in the Safety Data Tables and Figures, Table 14.3, as total treatments across the replicate dosing schedule. Exposure data here are provided as in the clinical study report (INS-10-012 and INS-12-015). Note that numbers of subjects taking Dronabinol Oral Solution and Marinol[®] Capsules are presented differently in the ISS, as 86 subjects each taking two doses of Dronabinol Oral Solution and as 87 subjects each taking two doses of Marinol[®] Capsules.

Clinical Review
Wen-Yi Gao, MD, PhD
NDA 205,525/000
Syndros (Dronabinol Oral Solution)

6) Study INS-004-15-059

Title of Study: 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

Study Design: This was an open-label, randomized, six-sequence, single-dose, three-period crossover study with a planned enrollment of 54 subjects to compare the bioavailability of dronabinol oral solution, 4.25 mg when administered under fed conditions compared to Marinol capsules, 5 mg administered under fed and fasted conditions in healthy males and non-pregnant females.

Subjects were assigned numbers in an ascending order, based on successful completion of the screening process. 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 drug administration was separated by a washout period of 7 days.

Subjects received Treatments A and B after a 10 hour overnight fast followed by consumption of a FDA standard high-calorie, high-fat breakfast meal beginning 30 minutes prior to study drug administration. Subjects received Treatment C after a 10 hour overnight fast. No food was allowed until 4 hours after dose administration.

During each study period, 6 mL blood samples were obtained for pharmacokinetic analyses from all subjects prior to each dose and at selected times through 48 hours post dose.

Study Centers: Worldwide Clinical Trials Early Phase Services, LLC (WCT), 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217

Test Products:

Treatment A: Dronabinol Oral Solution 4.25 mg/0.85 mL

Treatment B: Marinol Capsules 5 mg, under fed conditions

Treatment C: Marinol Capsule 5 mg, under fasted conditions

Dose = Dronabinol Oral Solution 4.25 mg (1 x 4.25 mg/0.85 mL) with 240 mL water, Marinol Capsules 5 mg (1 capsule)

Duration of Treatment: Three single dose treatments were administered with a 7-day washout period between doses

Clinical Review
Wen-Yi Gao, MD, PhD
NDA 205,525/000
Syndros (Dronabinol Oral Solution)

Safety Findings: No deaths, no serious adverse events (SAEs) were reported from the 3 treatment groups over the course of this study. Treatment-emergent adverse events (TEAEs) were 9 (17%) subjects in Treatment A, 9 (17%) subjects in Treatment B, 12 (22%) subjects after administration of Treatment C. One subject (Subject 0011073) in Treatment C was withdrawn from the study due to an AE (vomiting).

The most commonly reported TEAE was headache; reported by 2 (3.8%) subjects in Treatment A, 1 (1.9%) subject in Treatment B, and 2 (3.8%) subjects in Treatment C. The second most commonly reported TEAE was euphoric mood: 2 (3.8%) subjects in Treatment A and 1 (1.9%) subject in Treatment C.

All of the AEs were mild in severity. There were no moderate or severe AEs reported. None of the AEs were related to abnormal laboratory evaluations. No clinically significant abnormalities in vital signs or physical exams were observed. A summary of all treatment emergent AEs reported over the course of the study is presented in Table 1.

Table 1 (INS-004-15-059): Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

MedDRA Primary System Organ Class	MedDRA Preferred Term	Number of Subjects Reporting		
		Treatment A (N=52)	Treatment B (N=54)	Treatment C (N=53)
Gastrointestinal disorders	Nausea	0 (0.0)	0 (0.0)	1 (1.9)
	Paraesthesia oral	1 (1.9)	0 (0.0)	0 (0.0)
	Vomiting	0 (0.0)	0 (0.0)	1 (1.9)
	Dental caries	0 (0.0)	1 (1.9)	0 (0.0)
General disorders and administration site conditions	Hunger	0 (0.0)	0 (0.0)	1 (1.9)
	Thirst	0 (0.0)	0 (0.0)	1 (1.9)
	Vessel puncture site pain	0 (0.0)	0 (0.0)	2 (3.8)
	Fatigue	1 (1.9)	1 (1.9)	0 (0.0)
Infections and infestations	Rash pustular	0 (0.0)	1 (1.9)	0 (0.0)
	Upper respiratory tract infection	0 (0.0)	1 (1.9)	0 (0.0)
	Pharyngitis bacterial	0 (0.0)	0 (0.0)	1 (1.9)
Injury, poisoning and procedural complications	Wound	1 (1.9)	0 (0.0)	0 (0.0)
Nervous system disorders	Headache	2 (3.8)	1 (1.9)	2 (3.8)
	Presyncope	0 (0.0)	0 (0.0)	1 (1.9)
	Somnolence	0 (0.0)	1 (1.9)	0 (0.0)
	Dizziness	0 (0.0)	1 (1.9)	0 (0.0)
Psychiatric disorders	Euphoric mood	2 (3.8)	0 (0.0)	1 (1.9)
	Anxiety	0 (0.0)	1 (1.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	0 (0.0)	0 (0.0)	1 (1.9)
	Rhinitis allergic	1 (1.9)	1 (1.9)	0 (0.0)
Skin and subcutaneous tissue disorders	Urticaria	1 (1.9)	0 (0.0)	0 (0.0)

Treatment A = Dronabinol oral solution, 4.25 mg, under fed conditions
Treatment B = Marinol (dronabinol) capsule, 5 mg, under fed conditions
Treatment C = Marinol (dronabinol) capsule, 5 mg, under fasted conditions
MedDRA = Medical Dictionary for Regulatory Affairs, Version 18.1; Source: [Table 14.3.1.2](#)

13.4. Literature Review

Literature Review focuses on the safety and effectiveness of Droabinol Capsules (Marinol) treatment in HIV infected and CINV patients.

- 1) Bedi Study:
 - a. Design:

Clinical Review

Wen-Yi Gao, MD, PhD

NDA 205,525/000

Syndros (Dronabinol Oral Solution)

This was a double-blind randomized placebo controlled crossover study of dronabinol given orally in seven patients who were HIV-positive. The mean age of the patients were 36.6 ± 1.3 years old (Ragen 29.0-39.0 y.o.); and smoked marijuana 4.2 ± 2.3 days/week. Each patient received daily oral doses of dronabinol capsules (10 mg qid) in one 8-day hospital stay and placebo in the other 8day hospital stay.

b. Efficacy variables:

Efficacy was assessed with:

- Food Intake: The food box was supplemented with frozen meals or extra items as required. Participants reported items eaten by scanning custom-designed bar codes that recorded time, calories, and macronutrient content for individual items. Self-reports were confirmed by observation, and daily examination of trash.
- Body Weight: Participants were weighed each morning before breakfast.
- Subjective Hunger and Satiety: The Hunger-Satiety Questionnaire (HSQ) is a 6-item Visual Analogue instrument that assesses self-rated hunger, fullness, nausea, thirst, and dry mouth.
- Food Cravings: Desire for particular food types was assessed with the Food Desirability Questionnaire (FDQ; Evans et al. 1999), a self-report instrument listing 38 food types; participants use a 5-point scale, ranging from 0 ('not at all') to 4 ('extremely'), to rate the extent to which they would like each food type. FDQ items are grouped into six subscores: 1) savory carbohydrates/fats e.g. French fries, 2) sweet carbohydrates/fat e.g. cookies; 3) protein/fats e.g. cheese; 4) carbohydrates alone e.g. bread; 5) beverages; and 6) alcohol.
- Subjective Mood and Drug Effect: Assessments of self-reported mood and drug effects consisted of Visual Analogue Scales and a Drug Effects Questionnaire. The VAS included 44 mood ('mellow'), physical symptom ('chills') and drug effect ('high') descriptors; participants rated the extent to which each descriptor applied to them at that time. Based on previous cluster analyses (Haney, 2007), we employed arithmetic means of item scores to produce six subscales: Negative Affect (example item: 'miserable'); Anxiety ('on edge'); Somatic Symptoms ('upset stomach'); Sedation ('tired'); Positive Affect ('content'); and Drug High ('high'). The DEQ consisted of 5 items assessing the extent to which participants: felt a good drug effect; felt a bad effect; liked the effect; felt a strong effect; and would take the drug again.
- Sleep: Objective sleep quality was measured using a Nightcap sleep monitor, consisting of a portable amplifier attached to two leads, one attached to the forehead to measure body movement (participants were instructed to remain in bed overnight) and the second attached to eyelids to measure eye movement. Outcome measures included sleep latency, number of awakenings, and sleep efficiency (proportion of total bed time in Rapid Eye Movement [REM] and non-REM [NREM] sleep). Subjective sleep quality was measured with 7 Visual Analogue

Clinical Review

Wen-Yi Gao, MD, PhD

NDA 205,525/000

Syndros (Dronabinol Oral Solution)

Scales assessing perceived quality of sleep that were completed every morning after waking.

- Cognitive Function: A computerized task battery measured basic and higher-level neuropsychological functions including psychomotor function, simple and divided attention, information processing, and verbal and working memory. The battery included a 3-minute Digit-Symbol Substitution Task, a 10-minute Divided Attention Task, a 10-minute Rapid Information Processing Task, a 3-minute Rapid Acquisition Task, and a 2-minute immediate and delayed Digit Recall task.

- c. Results: Despite sustained increases in self-reported food cravings, dronabinol only increased caloric intake in the initial eight days of dosing. Similarly, sleep quality was improved only in the first 8 days of dosing. Dronabinol's mood-enhancing effects were sustained across the 16-day inpatient stay. Dronabinol was well tolerated, causing few negative subjective or cognitive effects.
- d. Conclusions: In HIV-positive marijuana smokers, high dronabinol doses safely and effectively increased caloric intake. However, repeated high-dose dronabinol appeared to result in selective tolerance to these effects. These findings indicate that HIV-positive individuals who smoke marijuana may require higher dronabinol doses than are recommended by the FDA. Future research to establish optimal dosing regimens, and reduce the development of tolerance, is required.

2) Haney Study:

a. Design:

This was a double-blind placebo controlled crossover study of dronabinol capsules given orally in 10 HIV-infected patients. Patients completed two 16-day inpatient phase; in between the inpatient phase, there was a washout phase (5 to 10 days) as outpatient. Each dronabinol (5 and 10 mg) and marijuana (2% and 3.9% Δ^9 -tetrahydrocannabinol (THC) dose was administered 4 times daily for 4 days, but only 1 drug was active per day, thereby maintaining double-blind dosing. The mean age of the patients was 40.1 ± 1.9 years old.

b. Efficacy variables:

- As compared with the placebo, the daily caloric intake and body weight of HIV-patients who receiving marijuana or dronabinol were increased in a dose-dependent manor.
- Intoxication (i.e., "good drug effect" by rating) was observed.
- Effects of marijuana and dronabinol were comparable.

c. Conclusion:

Dronabinol and marijuana were well tolerated and produced substantial increases in food intake.

Clinical Review

Wen-Yi Gao, MD, PhD

NDA 205,525/000

Syndros (Dronabinol Oral Solution)

3) Meiri Study:

a. Design:

This was a double-blind, placebo-controlled 5-day study to evaluate the antiemetic effects and safety of oral dronabinol alone and in combination with ondansetron versus ondansetron alone in patients (n = 64) receiving moderately to highly emetogenic chemotherapy. Patients received dronabinol doses (2.5 mg and 5 mg PO qid) and other ondansetron (4 mg and 8 mg bid). Episodes of vomiting or retching were defined as instances of vomiting or retching separated by ≥ 1 minute.

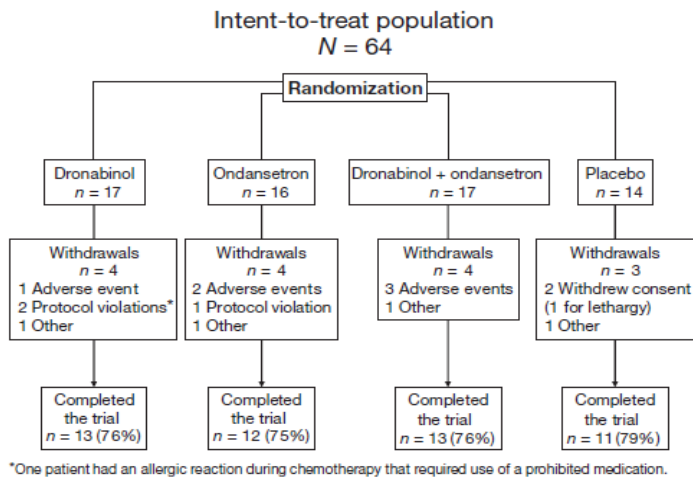
Primary outcome measure

The primary efficacy measure was the incidence of total response to treatment following administration of moderately to highly emetogenic chemotherapeutic agents. Total response was defined as no vomiting and/ or retching, intensity of nausea < 5 mm on a 100-mm Visual Analog Scale (VAS scale 0–100 mm; 0 mm = no nausea; 100 mm = intractable nausea), and no use of rescue medication.

Table 1 (Meiri): Dosing Schedule

Treatment group	Day 1		Day 2 (fixed dose)	Days 3–5 (flexible dose)
	Prechemotherapy	Postchemotherapy		
Dronabinol	Dexamethasone 20 mg PO Ondansetron 16 mg IV Dronabinol 2.5 mg PO	Dronabinol 2.5 mg PO	Dronabinol 2.5 mg PO QID (10 mg/day)	Dronabinol 2.5–5 mg PO QID (10–20 mg/day)
Ondansetron	Dexamethasone 20 mg PO Ondansetron 16 mg IV Dronabinol 2.5 mg PO	Dronabinol 2.5 mg PO	Ondansetron 8 mg PO BID (16 mg/day)	Ondansetron 4–8 mg PO BID (8–16 mg/day)
Combination	Dexamethasone 20 mg PO Ondansetron 16 mg IV Dronabinol 2.5 mg PO	Dronabinol 2.5 mg PO	Dronabinol 2.5 mg PO QID (10 mg/day) + Ondansetron 8 mg PO BID (16 mg/day)	Dronabinol 2.5–5 mg PO QID (10–20 mg/day) + Ondansetron 4–8 mg PO BID (8–16 mg/day)
Placebo	Dexamethasone 20 mg PO Ondansetron 16 mg IV Placebo PO	Placebo PO	Placebo PO QID	Placebo PO QID

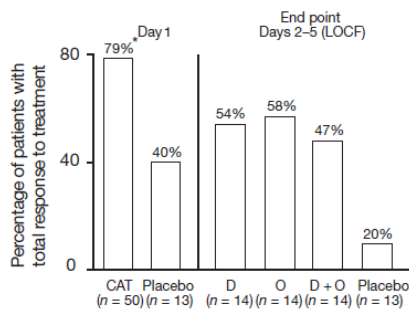
BID = twice daily; IV = intravenously; PO = by mouth; QID = four times daily



b. Efficacy Outcomes:

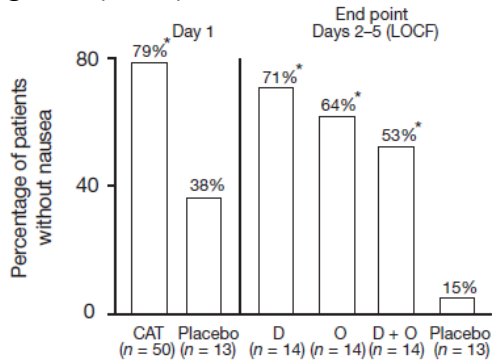
Total response is shown in Figure 1. Comparisons between placebo and other treatment groups were not statistically significant, essentially because of the small sample size. However, the improvement (range: 47–58%) in the three active treatment groups compared with placebo (20%) implies clinically relevant improvement (days 2–5 LOCF).

Figure 1 (Meiri): Total response during active treatment



Note: Day 1 results were separated from Days 2-5 with the vertical line. *p < 0.05 vs. placebo. CAT = combined active treatment; D = dronabinol; D + O = combination; LOCF = last observation carried forward; O = ondansetron; P = placebo

Figure 2 (Meiri): Absence of nausea during active treatment



Note: Day 1 results are separated from Days 2-5 with the dvertical line. *p < 0.05 vs. placebo. CAT = combined active treatment; D = dronabinol; D + O = combination; LOCF = last observation carried forward; O = ondansetron; P = placebo

c. Adverse Events:

All serious adverse events were determined to be unrelated to study medication. No clinically significant changes were observed in laboratory values, blood pressure (< 10 mmHg vs. baseline), pulse, temperature, or weight.

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/s/

WEN-YI GAO
04/01/2016

STEPHANIE O OMOKARO
04/01/2016