CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202788Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	202-788
Drug Name:	Subsys (Fentanyl) Sublingual Spray
Indication(s):	Management of breakthrough cancer pain in opioid tolerant patients with malignancies
Applicant:	Insys Therapeutics, Inc.
Date(s):	Letter date: March 4, 2011, PDUFA date: January 4, 2012
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Yan Zhou, Ph.D.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Analgesia, Anesthesia and Addiction Products
Clinical Team:	Luke Yip, M.D. Sharon Hertz, M.D.
Keywords:	Clinical Studies, cross-over design, ANOVA, permutation test

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1. EXECUTIVE SUMMARY

Insys Therapeutics Inc. submitted a New Drug Application for Subsys (fentanyl) sublingual (b) (4) seeking approval for the proposed indication of "management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain." I conclude that evidence from the efficacy study was statistically in favor of Subsys in comparison to placebo as measured by the sum of pain intensity difference from baseline to 30 minutes after dosing (SPID30).

The submission contained one efficacy study, INS-05-001, which was a multi-center, crossover study to evaluate the safety and efficacy of Subsys. Subjects who successfully titrated during an open-label titration phase then entered into a randomized, double-blind, placebo-controlled phase of up to 26 days, during which 10 episodes of breakthrough pain were treated with Subsys (7 episodes) or placebo (3 episodes).

The primary objective of the double-blind phase was to assess the analgesic efficacy of Subsys. The primary efficacy endpoint was the summed pain intensity difference at 30 minutes after dosing. Secondary endpoints were total pain relief at 30 minutes, subject's global evaluation of study medication at 30 minutes and pain intensity difference (PID) at different time points.

The applicant calculated the mean of the primary efficacy variable SPID30 across episodes for each treatment and then analyzed the difference between two averaged values using an analysis of covariance (ANCOVA) model with the mean baseline pain intensity across all episodes as a covariate. Similar analyses were performed for secondary endpoints. There was a concern that the design might not be balanced with respect to the episodes and that the analyses did not account for the correlated measurements from each subject. Thus, the agency requested the applicant submit analyses of SPID30 using an analysis of variance (ANOVA) model with fixed effects for treatment, episode, sequence and a random effect for subject. In response, the applicant submitted their re-analyses of SPID30. In addition, the applicant also conducted a permutation test to confirm their primary analysis based on the ANOVA model.

The applicant defined the Intent-to-Teat (ITT) population as all randomized subjects who took at least one dose of study medication and had at least one pain measurement following administration of study medication. The efficacy analysis set included all subjects in ITT population who took at least one breakthrough pain episode treated with Subsys and another treated with placebo. This analysis set was acceptable because an exclusion of subjects who received only one treatment in a crossover design would not lead to the same bias in estimating the treatment effect as in a parallel design study. In the study, one subject did not take the assigned sequence, but had pain intensity (PI) recorded for all 10 episodes. Two subjects did not take their assigned treatments for some episodes (one subject with 5 episodes and another subject with 3 episodes). The applicant did not include these episodes in their analyses. To make use of all available information, I included these 18 episodes in my analyses.

Based on my review, I conclude that Subsys reduced the pain intensity in patients with breakthrough cancer pain when compared to placebo.

2. INTRODUCTION

2.1 Overview

Fentanyl, the active ingredient in Subsys, is an opioid analgesic. Oral transmucosal fentanyl citrate (Actiq), fentanyl citrate buccal tablet (Fentora) and fentanyl citrate buccal film (Onsolis) have been approved for the management of breakthrough pain in opioid tolerant patients with cancer. Subsys is a sublingual (SL) spray formulation of fentanyl citrate designed for oral administration. According to the applicant, "Fentanyl SL Spray is expected to provide analgesic benefit to patients in an easy-to-use rapid-onset format." The clinical development program and statistical analyses were discussed at several meetings. At the pre-IND meeting on August 25, 2005 (under IND 72,411), the agency stated that one adequate and well-controlled study would be needed to investigate the use of Subsys in patients with breakthrough cancer pain. At the End-of-Phase 2 meeting on December 17, 2007, the applicant proposed a linear mixed model with fixed effects for treatment and time as the main efficacy analysis method. The agency stated that the benefit of including an effect for time was unclear and interest would be in the ANCOVA model results. The applicant also stated that the baseline observation carried forward (BOCF) method would be used to impute pain intensity at time points after the use of supplemental medication. The agency stated that the missing data concern in the crossover study design is not the same as in the setting of parallel group chronic pain trials. (b) (4) would not be included in the labeling. The following is quoted from the meeting minutes.

Question 2a
Insys proposes, as the main analysis method for the primary efficacy measure and related endpoints, using a repeated measures linear mixed model, and treating data at time points after the use of supplemental ("rescue") medication as missing. Additionally we will perform sensitivity analyses, including those using imputation, to assess how conclusions about treatment effect depend on the handling of data after use of supplemental medication. Since we understand, in some instances, that the agency has adopted the baseline observation carried forward (BOCF) approach for such data, we will use BOCF to impute pain intensity at time points after the use of supplemental medication, and analyze the within subject treatment summary using the Wilcoxon signed rank test. Does the agency agree with this statistical approach?

FDA Response
The Division's concern regarding missing data has primarily been in the setting of parallel group, chronic pain trials. In such trials, patients receive treatment for 12 weeks. Patients may experience some reduction in pain intensity, however, they drop out of the study because of intolerable side effects. The Division has advocated using missing data strategies that assign a bad score to patients experiencing unfavorable outcomes.

You propose a crossover study design where patients assess pain intensity for 30 minutes following each treatment administration. The missing data concern is not the same as in the setting of parallel group chronic pain trials.

In general, a linear mixed model is an acceptable approach for analyzing the data. Your model will include fixed effects for treatment and time. The benefit of including an effect for time is unclear. Including terms for sequence and/or period may be more beneficial. Additional comments will be provided once the protocol and statistical analysis plan have been submitted.

Sponsor Reply (provided prior to Industry Meeting)
Insys noted FDA's comment that the "benefit of including an effect for time is unclear." Insys would like to clarify how the time effect is needed to identify the 30-minute time point of our main efficacy endpoint, As noted on p. 29 of the briefing document, the primary efficacy endpoint, i.e., the summed Page 7 IND 72,411 Insys Therapeutics Inc. EOPII Meeting Minutes Fentanyl Sublingual Spray pain intensity differences at 30 minutes [SPID(30)], is defined mathematically as a linear combination of pain intensity (PI) at time points up and including 30 minutes.
Specifically:
`SPID(30) = 30*PI(0) – 5*PI(5) – 5*PI(10) – 5*PI(15) – 15*PI(30).`

However, rather than pre-calculating SPID(30) before statistical analysis, which might require imputation for missing data, we have chosen to implement the mathematical definition within the modeling and to allow the modeling to handle missing data automatically in the normal course of model fitting, without external imputation rules.

To see how this might work, consider an implementation of the mixed model using SAS, with PI as dependent variable and with the treatment (TRT) and time (TIME) factors as fixed effects. Suppose the levels of TRT are coded as 0 = Placebo and 1= Fentanyl SL Spray, and the levels of TIME as 0, 5, 10, 15, 30, 45 and 60 (minutes). Given the model parameters and SPID as a function of PI, a statement in SAS to assess the treatment effect with respect to SPID(30) is:

```
Contrast "Trt effect SPID(30)" TRT*TIME -30 5 5 5 15 0 0 30 -5 -5 -5 -15 0
0;
```

Insys noted the comment that "including terms for sequence and/or period may be beneficial." In the current analysis plan, the period effect is considered random, nested within subject. As a sensitivity analysis we will model period as a fixed effect, crossed with the subject effect. Also, there are 29 sequences, i.e., 29 different orderings of 3 placebo and 7 Fentanyl SL Spray treatments to which a subject may be randomized; we will examine the sequence effect descriptively.

Insys noted the comment that "additional comments will be provided once the protocol and statistical analysis plan have been submitted." Insys submitted the statistical analysis plan at the agency's request on December 5. If any questions or comments remain after our teleconference on December 17, Insys will look forward to hearing and discussing them.

Discussion
Ms. Meaker noted that the Agency's comment was related to the fact that linear models are often employed for longer study timepoints, so the Division was not sure these were the appropriate models to utilize. However, from the draft statistical analysis plan (SAP) the firm shared by email, she understands that the Agency will see both this analysis and the ANCOVA for the SPID (30) endpoint.

This is acceptable with the understanding that the Agency is interested first in the ANCOVA model results. Ms. Meaker stated that it is acceptable for the sponsor to conduct mixed-model imputation as a sensitivity analysis, noting that any discrepancies will need to be discussed in the study report.

The sponsor stated that they will amend their SAP based on the comments received and officially submit it to the IND.

During the August 17, 2010 pre-NDA meeting, the agency restated that a graphical representation of the primary efficacy endpoint (b) (4) may be included in the labeling.

Study INS-05-001 was designed to comply with the agency's requirement and support the application. My statistical review focuses on Study INS-05-001 which was a double-blind, randomized, placebo-controlled, multi-center, crossover trial.

Table 1: list of the study included in analyses

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design	Duration of Treatment
INS-05-001 (10/2007 – 02/2010)	35 centers (All US)	Titration: n = 130 Randomization: Subsys n= 98 Placebo n= 98	Placebo	Randomized, Double-blind, Cross-over, Placebo-controlled, Multicenter with an open-label titration phase	Titration: 26 days Double-Blind Treatment: 26 days

2.2 Data Sources

The initially submitted data can be found at \\Cdsesub1\evsprod\NDA202788\0003\m5\datasets. The applicant submitted datasets containing the raw data from the Case Report Form (CRF) as well as the derived analysis datasets. The datasets were not provided in SDTM or AdaM format. The applicant didn't submit analysis-ready datasets initially. On April 8, 2011, we requested the applicant submit analysis-ready datasets. The applicant submitted additional datasets per the Division's request, which can be accessed at \\Cdsesub1\evsprod\NDA202788\0007\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The resubmitted define document for the datasets clearly specified the source or the derivation of most variables. I was able to reproduce the secondary variables of interest as well as the primary outcome.

3.2 Evaluation of Efficacy

Study Design and Endpoints

After identification of an effective Subsys dose in the open-label titration phase, eligible subjects entered the double-blind phase. Each subject was given 10 doses of study medication, 7 doses of Subsys sublingual spray at the stable dose identified during the titration phase and 3 matching placebo doses. The ordering of Subsys and placebo doses was determined at random. There were totally 29 possible treatment sequences, and each patient was randomly assigned to one of them. The PI was assessed by the subject using a 0-100 mm visual analog scale (VAS), where one anchor represented no pain and the other reflected the worst possible pain. The PI was assessed at the following times during each breakthrough pain episode: 0, 5, 10, 15, 30, 45 and 60 minutes.

One hundred and sixty-one subjects were enrolled from 35 sites in the United States. One hundred and thirty subjects entered into the titration phase. Ninety-eight subjects achieved an

individualized successful dose during the titration phase and were randomized to one of 29 sequences with 10 treatment episodes.

The primary objective of the study was to demonstrate the superiority in analgesic efficacy of Subsys sublingual spray compared to placebo. The primary efficacy endpoint was the summed pain intensity difference from baseline to 30 minutes after dosing. Secondary endpoints included total pain relief at 30 minutes, subject's global evaluation of study medication at 30 minutes and pain intensity difference at different time points.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of subjects is shown in Table 2. A total 161 subjects were enrolled into the study. Among 98 randomized subjects, 3 subjects discontinued prior to completing the study, 1 due to adverse events (AE), 1 due to subject's decision and 1 did not comply with the protocol.

Table 2: Patient Disposition

	Number (%) of Patients
Screened	161
Titrated	130
Randomization	98 (100)
ITT*	96 (98)
Completed	95 (97)
Completed 10 episodes	79 (81)
Discontinued	3 (3)
Adverse events	1 (1)
not complied with protocol	1 (1)
Subject's decision	1 (1)

Source: Reviewer's Analyses
*Two subjects (114001, 119003) have no efficacy data due to an equipment malfunction

The demographic and baseline characteristics for ITT population are shown in Table 3. The majority of the subjects were white (91%), and the mean age was 54 years.

Table 3: Baseline Demographic Characteristics for ITT population (N=96)

Age (years)	
Mean (SD)	54 (12)
Range	24-85
Age Group (years), n (%):	
< 65	80 (83%)
>=65	16 (17%)
Race, n (%)	
White	87 (91%)
Black or African American	7 (7%)
Native Hawaiian or Other Pacific Islander	1 (1%)
American Indian or Alaskan Native	1 (1%)
Other	1 (1%)
Gender, n (%)	
Female	52 (54%)
Male	44 (46%)

Source: Clinical Study Report Table 14.1.4

Statistical Methodologies

The applicant's analyses for the primary efficacy endpoint, SPID30, were based on the mean of SPID30 across episodes for each treatment. For each subject, SPID30 of the 7 episodes treated with Subsys were averaged into a single value and SPID30 of the 3 episodes treated with placebo were averaged into a single value and the difference of these two averaged values was then analyzed by using an ANCOVA model with the mean baseline pain intensity across all episodes as a covariate. During the review, I requested the applicant submit analyses of SPID30 using an ANOVA model with fixed effects for treatment, episode, sequence and a random effect for subject. The requested analysis appropriately accounts for the correlation that arises from multiple measurements coming from each subject. Responding to the information request, the applicant submitted their re-analyses of SPID30. During the review, a permutation test on the primary comparison was also requested due to the possibility of confounding with an unbalanced randomization scheme. The applicant responded to the request and performed the permutation test. The test confirmed their primary results based on the ANOVA model.

The ITT population was defined as all randomized subjects who took at least one dose of study medication and had at least one pain measurement following administration of study medication. All efficacy analyses were based on the efficacy analysis set which included all subjects in ITT population who took at least one breakthrough pain episode treated with Subsys and another treated with placebo. Among 96 subjects in the ITT population, 4 subjects only took episode(s) of one treatment. The applicant's efficacy analysis set did not include these 4 subjects. In the review, I found among these 4 subjects, 1 subject did not take the assigned sequence, but had PI recorded for all 10 episodes. My analysis set included this subject. In addition, the applicant did not include 8 episodes in which subjects did not take their assigned treatments. To make use of all available information, I included these 8 episodes in my analyses.

Efficacy data recorded after rescue medication was taken for an episode were disregarded, and the missing values were imputed using the last observation carried forward method (LOCF) for that episode. For subjects that discontinued from the study during an episode, LOCF was used for that episode. Missing values in episodes after dropout were not imputed at all and subsequent episodes were excluded from the analyses.

Results and Conclusions

I replicated the applicant's primary analysis. In both the applicant's analysis (Table 4) and my analysis (Table 5), Subsys sublingual spray was statistically significantly different from and superior to placebo in terms of the primary efficacy variable SPID30. The secondary endpoints were also favorable for Subsys sublingual spray. In the study, 57 subjects took rescue medication. Only 14 subjects took rescue medication during the initial 30 minutes.

Table 4: Applicant's Primary Efficacy Re-Analysis

SPID30	Subsys Sublingual Spray (N of subjects = 92) (N of episodes = 620)	Placebo (N of subjects = 92) (N of episodes = 266)
LSMEANS (SE)	656 (43)	394 (47)
Difference from Placebo 95% CI		
P-value*	< 0.0001	

Source: study report: Table 14.2.21

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence and a random effect subject

Table 5: Reviewer's Primary Efficacy Analysis

SPID30	Subsys Sublingual Spray (N of subjects = 93) (N of episodes = 632)	Placebo (N of subjects = 93) (N of episodes = 272)
LSMEANS (SE)	644 (41)	387 (45)
Difference from Placebo (SE) 95% CI	257 (29) (200, 315)	
P-value*	< 0.0001	

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence and a random effect subject

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Luke Yip. The reader is referred to Dr. Yip's review for information regarding the adverse event profile. Safety risks appear consistent for this drug type.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

My subgroup analyses didn't reveal any issues that were concerning. The SPID30 was higher for Subsys across the subgroups including gender and age.

4.1 Gender, Race, Age, and Geographic Region

The applicant performed subgroup analyses for gender (female and male), age (<60 and ≥60 years, <65 and ≥65 years, and <75 and ≥75 years), race, type of around-the-clock pain medication used, type of prior breakthrough pain medication used, and successful dose of Subsys in their original analyses but did not perform subgroup analyses using the agency-requested analyses. I conducted subgroup analyses for gender (female and male) and age (<65 and >=65). Race was not included in the assessment of subgroups because the majority of the study population was white. In my analyses, I utilized the same ANOVA model with additional terms for each demographic variable and its interaction with treatment.

There was no statistically significant interaction between gender and treatment. Although there was a statistically significant interaction between age and treatment, for both age groups the mean of SPID30 was greater in the Subsys group compared to the placebo group.

Table 6: Reviewer's Subgroup Analyses for SPID30

	Subsys		Placebo	
Endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**
SPID30				
Gender				
Female	50	621 (514)	50	401 (493)
Male	43	667 (634)	43	388 (529)
Age (years)				
< 65	77	667 (594)	77	390 (521)
>= 65	16	525 (447)	16	415 (453)

4.2 Other Special/Subgroup Populations

No other subgroup analyses were requested by Dr. Yip.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant calculated the mean of the primary efficacy endpoint SPID30 across episodes for each treatment and analyzed the difference between two averaged values by using an ANCOVA model. Since the study design may not have been balanced with respect to the episode effect, the division requested the applicant conduct an additional analysis of SPID30 by using an ANOVA model with fixed effects for treatment, episode, sequence and a random effect subject. This requested analysis also accounted for the correlation among measurements that is apparent in crossover studies. A permutation test was also requested by the division to address the concern that the randomization scheme may not be balanced. In response, the applicant re-analyzed SPID30 by using the requested ANOVA model and performed the requested permutation test which confirmed their primary results based on the ANOVA model.

The applicant did not include 18 episodes in which subjects did not take their assigned treatments. I included these 18 episodes in my analyses to make use of all available information.

In the study, dropout was not a concern, and missing data were handled appropriately.

Since the applicant proposed a novel sublingual formulation of fentanyl, a well-known active substance for the treatment of pain, the division required demonstration of the efficacy in a single adequate and well-controlled clinical trial. The data from Study INS-05-001 provided statistically significant evidence of the efficacy of Subsys sublingual spray as a treatment of breakthrough pain in cancer patients.

5.2 Conclusions and Recommendations

The study reviewed provides adequate evidence of the analgesic effect of Subsys. Cancer patients receiving Subsys for breakthrough pain experienced a greater reduction in pain intensity compared to patients receiving placebo.

5.2.1 Labeling

The applicant submitted the following wording for the draft label:

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Signature/Distribution List

Primary Statistical Reviewer: Yan Zhou, Ph.D.
Mathematical Statistician

Date: November 18, 2011

Concurring Reviewer: Dionne Price, Ph.D.
Team Leader

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/s/

YAN ZHOU
11/30/2011

DIONNE L PRICE
11/30/2011
Concur

Statistics Filing Checklist of New NDA
Division of Biometrics II

Date: 4/26/11

NDA #: 202-788 Priority Classification: S

Proposed Trade Name: SUBSYS Applicant: Insys Therapeutics, Inc.

Generic Name: Fentanyl Sublingual Spray Date of Submission: 3/4/11

Indication: for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

No. of Controlled Studies: 1

User Fee Goal Date: 1/4/12

Date of 45-Day Meeting: 4/13/11

Medical Officer: Yip, Luke, M.D. (DAAP)

Project Manager: Davies, Kathleen (DAAP)

Statistical Reviewer: Zhou, Yan, Ph.D.

Statistical sections: Sections 2.5, 2.7, and 5.3.5

Anticipated Review Completion Date: 11/30/11

Comments:

1. It is fileable.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**NA**
Appropriate references included for novel statistical methodology (if present)	**NA**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Data from primary studies in electronic data room	**Yes**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design	Duration of Treatment
INS-05-001 (10/07 – 2/10)	35 centers (All US)	Titration: n = 130 Randomization: Fentanyl n= 98 Placebo n= 98	Placebo	Randomized, Double-blind, Cross-over, Placebo-controlled, Multicenter with an open-label titration phase	Titration: 26 days Double-Blind Treatment: 26 days

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Zhou, Yan
Mathematical Statistician

Concur: Price, Dionne, Ph.D.
Team Leader

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/s/

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05/03/2011

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