CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022510Orig1s000

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:	22-510
Drug Name:	ABSTRAL (fentanyl citrate) Sublingual Tablets
Indication(s):	Management of breakthrough pain in opioid tolerant patients with cancer
Applicant:	ProStrakan, Inc.
Date(s):	Submitted: August 5, 2009 PDUFA: June 2, 2010
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Yan Zhou, Ph.D.
Concurring Reviewers:	Dionne Price, Ph.D. Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia and Rheumatology Products
Clinical Team:	Frank Pucino, M.D.
Project Manager:	Kimberly Compton, R.Ph.
Keywords:	Clinical Studies, cross-over design, ANOVA, permutation test

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant seeks approval to market ABSTRAL (fentanyl citrate) sublingual tablets for the proposed indication of "management of breakthrough pain in cancer patients who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain."

The applicant conducted one controlled clinical study to support the efficacy of ABSTRAL for the proposed indication. Based on my review, I conclude that the study successfully demonstrated the superiority of ABSTRAL over placebo as measured by the sum of pain intensity difference from baseline to 30 minutes after dosing (SPID30).

1.2 Brief Overview of Clinical Studies

Fentanyl citrate, the active ingredient in ABSTRAL, is an opioid analgesic. Oral transmucosal fentanyl citrate (ACTIQ) and fentanyl citrate buccal tablets (FENTORA) have been approved for the management of breakthrough pain in opioid tolerant patients with cancer. ABSTRAL is a sublingual tablet formulation of fentanyl citrate designed for oral transmucosal delivery. According to the applicant, "The product offers a simple and predictable way of delivering fentanyl transmucosally while providing rapid disintegration and retaining the fast onset and individualized dose-titration aspects of the existing approved products." The clinical development program, endpoints and statistical analyses were discussed at several meetings. It was agreed between the applicant and the agency that one adequate and well controlled phase 3 study would be required for approval as 505(b)(2) application.

Study EN3267-005 was a double-blind, randomized, placebo-controlled, multi-center, crossover trial to investigate the safety and analgesic effect of ABSTRAL in opioid tolerant cancer patients. During an open-label titration phase, patients had up to 2 weeks to determine a single effective dose of ABSTRAL for adequate treatment of breakthrough pain. Patients who successfully titrated were then included in a double-blind, randomized, placebo-controlled phase of up to 2 weeks, during which 10 episodes of breakthrough pain were treated with ABSTRAL (7 episodes) or placebo (3 episodes). Patients who completed the double-blind phase could elect to continue in an open-label extension phase for up to 12 months.

The primary objective of the double-blind phase was to demonstrate the superiority in analgesic efficacy of ABSTRAL compared to placebo. The primary efficacy endpoint was the time-weighted summed pain intensity difference from baseline to 30 minutes after dosing. Secondary endpoints were summed pain intensity difference at 60 minutes, pain intensity difference (PID) at 10, 15, 30 and 60 minutes, pain relief, treated breakthrough pain episodes, and etc.

1.3 Statistical Issues and Findings

The analyses for the primary efficacy endpoint, SPID30, were based on the mean of SPID30 across episodes for each treatment. For each patient the 7 episodes treated with ABSTRAL were averaged into one value and the 3 episodes treated with placebo were averaged into one value and these averaged values were then analyzed by using an analysis of variance (ANOVA) model with fixed effects for treatment, pooled center, sequence and a random effect patient. No period effect was included because of the averaging across episodes (periods) for each patient. Similar analyses were performed for secondary endpoints. During the review, the agency requested the applicant submit analyses of SPID30 and including a fixed effect for episode into the ANOVA model. This request was based on a concern that the design might not be balanced with respect to the episodes or periods. In response, the applicant submitted their re-analyses of SPID30. In addition, instead of treating patient as a random effect as done in the initial analyses, the applicant treated patient nested within the sequence-by-pooled center interaction as a random effect in the re-analyses. This modification had no effect on the test for the fixed effects treatment and episode, but the tests for the fixed effects sequence and pooled center had different results. Since our primary objective was to test the treatment effect of ABSTRAL compared to the placebo, I analyzed SPID30 by using an ANOVA model with fixed effects for treatment, episode, pooled center, sequence and a random effect patient. Similar analyses were performed for SPID at 60 minutes and other secondary endpoints. No adjustment for multiplicity was made for the secondary analyses.

A permutation test on the primary comparison was recommended to the applicant during the End-of-Phase 2 meeting on September 21, 2005 (IND 69,190) due to the possibility of confounding with an unbalanced randomization scheme. The applicant didn't conduct the permutation test. After the information request was sent, the applicant responded and performed the permutation test. The test confirmed their primary results based on the ANOVA model.

There was an additional concern. To calculate the primary efficacy endpoint, SPID30, which was the time-weighted summed pain intensity difference at 30 minutes, the applicant used inconsistent timing for the assessment of pain intensity (PI) in the formulation. For PI assessed at 10 and 15 minutes after dosing, the actual observed time was used. While for PI assessed at 30 minutes after dosing, the scheduled time was used. To be consistent, I re-derived the SPID30 variable by using the actual observed time of PI assessed at 30 minutes after dosing.

The applicant planned an interim analysis at approximately 75% of the planned enrollment. The interim analysis was performed by an independent statistician not affiliated with the company. Pocock's group sequential procedure (Pocock, 1977) was applied to preserve the overall type I error rate of 0.05. With statistically significant efficacy results based on pre-specified criteria, a decision was made to stop randomization into the double-blind phase. At the time the interim analysis was performed, three additional patients were already enrolled in the double-blind treatment phase but data from these patients were not available for the interim analysis. The applicant did not include these three patients in their final analyses since they treated the

interim efficacy analyses as their primary efficacy analyses. To make use of all available information, I included these three patients in my analyses.

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

2. INTRODUCTION

2.1 Overview

ABSTRAL developed by ProStrakan Inc. is a sublingual tablet formulation of fentanyl citrate designed for oral transmucosal delivery. The applicant conducted 16 clinical studies (two phase 3, one phase 2, and thirteen phase 1) to support the efficacy and safety of ABSTRAL. At the pre-IND meeting on August 06, 2004 (under IND 69,190), the Food and Drug Administration (FDA) stated that one adequate and well-controlled study would be needed to investigate the use of ABSTRAL in patients with breakthrough cancer pain. Study EN3267-005 was designed to comply with this requirement and was the pivotal study that supported this application. Two additional studies provided further support for ABSTRAL: an open-label, long-term safety and effectiveness study of multiple doses of ABSTRAL (Study EN3267-007) and a phase 2 single-dose study (Study SuF-002). My statistical review focuses on the pivotal study (Study EN3267-005) which was a double-blind, randomized, placebo-controlled, multi-center, crossover trial.

2.2 Data Sources

The data and final study report for the electronic submission were archived under the network path location \\Cdsesub1\evsprod\NDA022510\0004. The applicant didn't submit analysis-ready datasets initially. On August 27, 2009, we requested the applicant submit analysis-ready datasets for all phase 2 and phase 3 studies. The applicant submitted the requested datasets for each study.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study EN3267-005 was a multi-center, randomized, double-blind, placebo-controlled, crossover study. After identification of a single effective ABSTRAL dose in the open-label titration phase, eligible patients entered the double-blind phase. Each patient was given 10 doses of study medication, with 7 doses of ABSTRAL sublingual tablets at the stable dose identified during the titration phase and 3 matching placebo doses. The ordering of ABSTRAL and placebo doses was determined at random. However, the randomization was subject to several restrictions. There was one placebo dose among the

first three doses, another among the second three doses and another among the last four doses, but placebo doses could not be consecutive. There were totally eight possible treatment sequences satisfying the restrictions, and each patient was randomly assigned to one of them.

Subjects were enrolled from 36 sites in the United States. Seventy-eight subjects achieved an individualized successful dose during the titration phase and sixty-six subjects were randomized to one of eight sequences with ten treatment periods.

The primary objective of the study was to demonstrate the superiority in analgesic efficacy of ABSTRAL sublingual tablets compared to placebo. The primary efficacy endpoint was the time-weighted summed pain intensity difference from baseline to 30 minutes after dosing. Secondary endpoints included summed pain intensity difference at 60 minutes, pain intensity difference at 10, 15, 30 and 60 minutes, pain relief, treated breakthrough pain episodes.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

The disposition of subjects is shown in Table 1. A total 131 patients were enrolled into the study. Among 66 randomized subjects, six patients discontinued prior to completing the study, two due to adverse events (AE) and another four due to other reasons.

Table 1: Patient Disposition

	Number (%) of Patients
Screened	136
Enrolled	131 (100)
Randomization	66 (50)
ITT	64 (49)
Completed	60 (46)
Discontinued	6 (5)
Adverse events	2 (2)
Lack of efficacy	0 (0)
Other	4 (3)
Protocol violation	2 (2)
Patient withdrew consent	2 (2)

Source: Reviewer's Analyses

The demographic and baseline characteristics are shown in Table 2. The majority of the subjects were white (85%), and the mean age was 53 years.

Table 2: Demographic Characteristics at Baseline (N=66)

Age (years)	
Mean (SD)	53 (11)
Range	21-80
Age Group (years), n (%):	
18-64	56 (85%)
65-74	9 (14%)
>74	1 (2%)

Race, n (%)	
White	56 (85%)
Black or African American	1 (2%)
Asian	2 (3%)
American Indian or Alaskan Native	1 (2%)
Hispanic or Latino	6 (9%)
Gender, n (%)	
Female	35 (53%)
Male	31 (47%)

Source: Clinical Study Report Table 5

3.1.3 Statistical Methodologies

The applicant analyzed the mean of the primary efficacy variable SPID30 using an ANOVA model with fixed effects for treatment, sequence, pooled center, and a random effect for patient. No period effect was included because of the averaging across episodes (periods) for each treatment within each patient. During the review, I requested the applicant submit analyses of SPID30 including a fixed effect for episode. Responding to the information request, the applicant submitted their re-analyses of SPID30. In addition, instead of treating patient as a random effect in the initial analyses, the applicant included patient nested within the sequence-by-pooled center interaction as a random effect in the re-analyses. This modification had no effect on the test for the fixed effects of treatment and episode.

The scheduled time for PI at 30 minutes was used to calculate the primary endpoint, SPID30. I re-derived SPID30 by using the actual observed time for PI at 30 minutes and re-analyzed SPID30 by using an ANOVA model similar to the applicant's model except the random effect was patient. The applicant also conducted the permutation test to confirm their primary analysis based on the ANOVA model.

All efficacy analyses were based on the intent-to-treat (ITT) population which included all randomized patients who received at least one dose of double-blind study medication and provided baseline and at least one post-baseline pain intensity score during the double-blind treatment phase.

The applicant planned an interim analysis at approximately 75% of the planned enrollment. The interim analysis was performed by an independent statistician not affiliated with the company. Pocock's group sequential procedure (Pocock, 1977) was applied to preserve the overall type I error rate of 0.05, and the nominal significance level was 0.0414 for the interim analysis. With statistically significant efficacy results based on pre-specified criteria, a decision was made to stop randomization into the double-blind phase and 12 additional enrolled patients who successfully completed the open-label titration phase were moved directly into the long-term extension phase to provide additional safety information. At the time the interim analysis was performed, three additional patients were already enrolled in the double-blind treatment phase but data from these patients were not available for the interim analysis. The applicant did not include these three patients in their final analyses since they treated the interim efficacy

analyses as their primary efficacy analyses. To make use of all available information, I included these three patients in my analyses.

Efficacy data recorded after rescue medication taken for an episode were disregarded and the missing values were imputed using the last observation carry forward method (LOCF) for that episode. For patients discontinued from the study during an episode due to an AE, baseline observation carry forward (BOCF) method was used for that episode. For patients discontinued from the study for any other reasons, 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. Intermediate missing values within an episode were imputed by using the linear interpolation method.

3.1.4 Results and Conclusions

In both the applicant's analysis (Table 3) and my analysis (Table 4), ABSTRAL sublingual tablets were statistically significantly different from and superior to placebo in terms of the primary efficacy variable SPID30. The secondary endpoints were also favorable for ABSTRAL sublingual tablets (Table 7 in Appendix).

Table 3: Applicant's Primary Efficacy Re-Analysis

SPID30	Abstral Sublingual Tablets (N of subjects = 61) (N of episodes = 393)	Placebo (N of subjects = 61) (N of episodes = 168)
LSMEANS (SE)	50 (4)	36 (4)
Difference from Placebo 95% CI	14 (8, 21)	
P-value*	< 0.0001	

Source: statistical report: study EN3267-005 efficacy re-analysis

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence, pooled center and a random effect patient nested within the sequence-by-pooled center interaction

Table 4: Reviewer's Primary Efficacy Analysis

SPID30_reviewer	Abstral Sublingual Tablets (N of subjects = 64) (N of episodes = 414)	Placebo (N of subjects = 64) (N of episodes = 177)
LSMEANS (SE)	52 (4)	36 (4)
Difference from Placebo 95% CI	16 (10, 22)	
P-value*	< 0.0001	

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

3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Frank Pucino. The reader is referred to Dr. Pucino's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The applicant performed subgroup analyses for gender (female and male) and age (18-64 and >65) in their original analyses, but did not perform subgroup analyses in the agency-requested re-analyses. I conducted subgroup analyses for gender (female and male) and age (18-64 and >65). Race was not included in the assessment of subgroups because the overall study population was largely 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. There was also no statistically significant interaction between age and treatment. Similar results were found for the secondary endpoints.

Table 5: Reviewer's Subgroup Analyses for SPID30

	ABSTRAL			Placebo	
Endpoint	**n**	**Mean (SD)**		**n**	**Mean (SD)**
SPID30					
Gender					
Female	33	53 (44)		32	36 (50)
Male	31	51 (42)		28	38 (46)
Age (years)					
18-64	55	53 (43)		52	36 (48)
>65	9	44 (47)		8	42 (48)

Table 6: Reviewer's Subgroup Analyses for SPID30_reviewer

	ABSTRAL			Placebo	
Endpoint	**n**	**Mean (SD)**		**n**	**Mean (SD)**
SPID30_reviewer					
Gender					
Female	33	54 (46)		32	36 (50)
Male	31	52 (43)		28	38 (46)
Age (years)					
18-64	55	54 (44)		52	37 (48)
>65	9	46 (48)		8	43 (48)

4.2 Other Special/Subgroup Populations

No other subgroup analyses were requested by Dr. Pucino.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

The applicant analyzed the mean of the primary efficacy endpoint SPID30 across episodes for each treatment by using an ANOVA model without period. Based on a concern that the study design may not have been balanced, the division requested the applicant conduct an additional analysis including episode effect in the model and conduct a permutation test. In response, the applicant re-analyzed SPID30 instead of the mean of SPID30 by using an ANOVA model with period. No matter which term was treated as a random effect, patient or patient nested within the interaction between sequence and pooled center, the test of the treatment effect was not be affected. The applicant performed the permutation test which confirmed their primary results based on the ANOVA model.

Additionally, the applicant used the scheduled time for the pain intensity assessment at 30 minutes to calculate the primary efficacy endpoint SPID30. I re-derived SPID30 by using the actual time of the pain intensity assessment at 30 minutes.

The applicant treated the interim efficacy analyses as their primary efficacy analyses. Their analyses did not include three patients who were already enrolled in the double-blind treatment phase at the time the interim analysis was performed. I included these three patients in my analyses to make use of all available information.

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

5.1.2 Collective Evidence

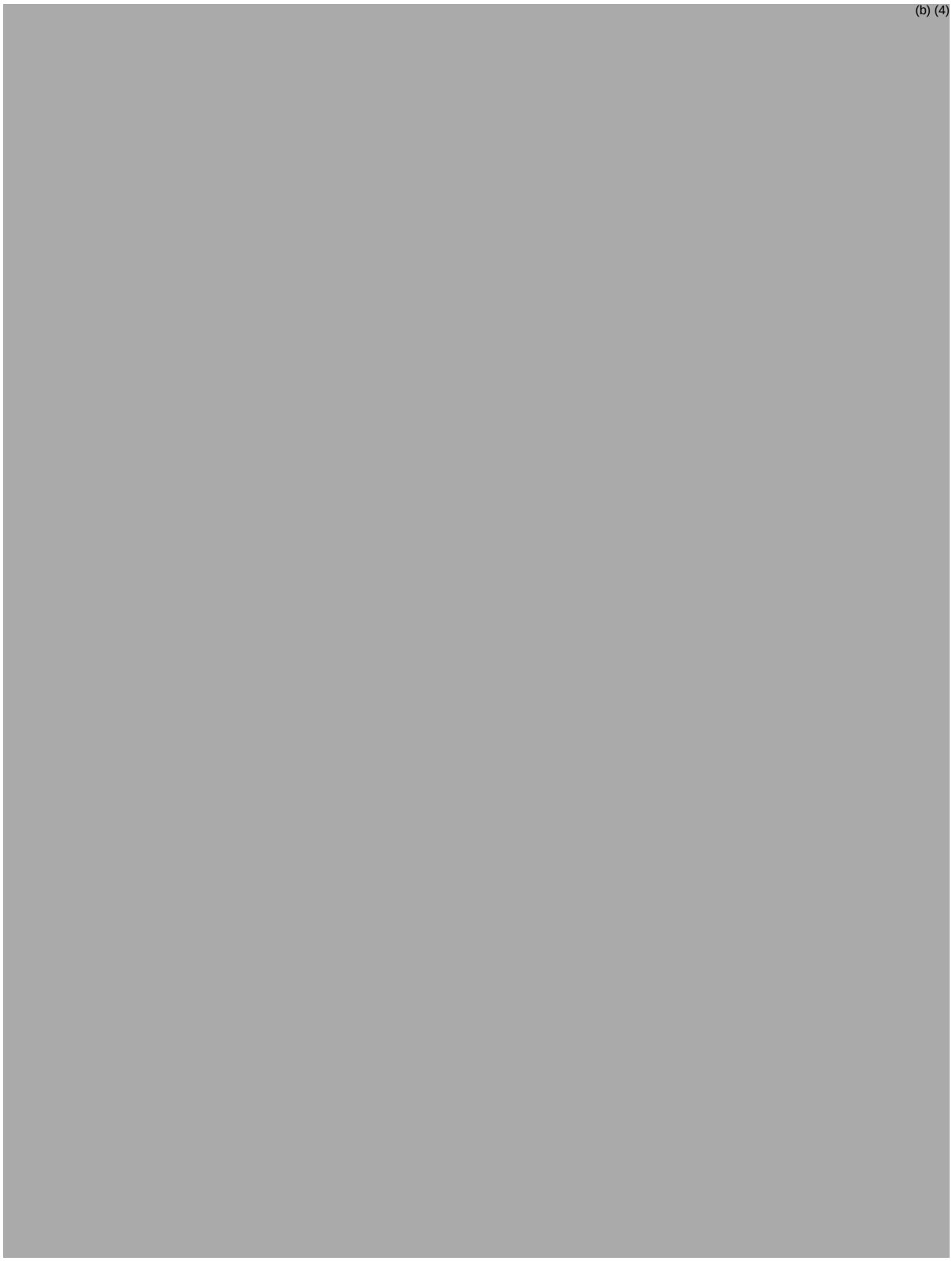
Since Prostrakan proposed a novel sublingual formulation of fentanyl, a well-known active substance for the treatment of pain, the division required demonstration of the efficacy in a single adequate and well-controlled clinical trial. The data from Study EN3267-005 provided statistically significant evidence of efficacy of ABSTRAL sublingual tablets as a treatment of breakthrough pain in cancer patients.

5.2 Conclusions and Recommendations

Based on my review, I conclude that cancer patients receiving ABSTRAL for breakthrough pain experienced a greater reduction in pain intensity compared to patients receiving placebo. The study reviewed provides evidence of the analgesic effect of ABSTRAL.

5.2.1 Labeling

The applicant submitted the following wording for the draft label:



(b) (4)

Suggestions for labeling:

We recommend the applicant not report the long-term safety study in this section of the label. (b) (4)

Appendix

Table 7: Applicant's Analyses of Secondary Efficacy Variables

	Abstral Sublingual Tablets (N of subjects = 61) (N of episodes = 393)	Placebo (N of subjects = 61) (N of episodes = 168)	p-value*
SPID60 LSMEANS (SE)	145.3 (9.5)	102.3 (10.9)	<0.0001
PID10 LSMEANS (SE)	1.2 (0.1)	0.9 (0.1)	0.0062
PID15 LSMEANS (SE)	2.0 (0.2)	1.4 (0.2)	<0.0001
PID30 LSMEANS (SE)	3.0 (0.2)	2.1 (0.2)	<0.0001
PID60 LSMEANS (SE)	3.8 (0.3)	3.3 (0.3)	0.0026

Source: statistical report: study EN3267-005 efficacy re-analysis

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence, pooled center and a random effect patient nested within the sequence-by-pooled center interaction

Signature/Distribution List

Primary Statistical Reviewer:	Yan Zhou, Ph.D. Mathematical Statistician
Date:	March 12, 2010
Concurring Reviewer:	Dionne Price, Ph.D. Team Leader
	Thomas Permutt, Ph.D. Division Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) (b) (4) tablets

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/s/

YAN ZHOU
03/12/2010

DIONNE L PRICE
03/12/2010
Concur

THOMAS J PERMUTT
03/12/2010
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Statistics Filing Checklist of New NDA
Division of Biometrics II

Date: 9/21/09

NDA #: 22-510 Priority Classification: S

Trade Name: ABSTRAL (b) (4) Applicant: ProStrakan, Inc.

Generic Name: Fentanyl citrate Date of Submission: 8/5/09

Indication: treatment of breakthrough pain in cancer patients who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain.

No. of Controlled Studies: 1

User Fee Goal Date: 6/4/10

Date of 45-Day Meeting: 9/16/09

Medical Officer: Pucino, Frank, MD (DAARP)

Project Manager: Compton, Kimberly (DAARP)

Statistical Reviewer: Zhou, Yan, Ph.D.

Statistical sections: Sections 2.5, 2.7, and 5.3.5

Anticipated Review Completion Date: 4/5/10

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	**Yes**
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, after an information request was sent to request the analysis-ready datasets**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes, except that race was not investigated because the overall study population was largely Caucasian.**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design	Duration of Treatment
EN3267-005 (1/06 – 12/08)	36 centers (All US)	Titration: n = 131 Randomization: Abstral n=64 Placebo n=64	Placebo	Randomized, Double-blind, Cross-over, Placebo-controlled, Multicenter with an open-label titration phase	Titration: 14 days Double-Blind Treatment: 14 days

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Zhou, Yan
Mathematical Statistician

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

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

/s/

YAN ZHOU
09/30/2009

DIONNE L PRICE
09/30/2009