CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-947

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 21-947

Drug Name: OraVescent Fentanyl Citrate

Indication(s): Management of breakthrough pain in opioid tolerant patients with cancer

Applicant: Cephalon, Inc. c/o CIMA Labs

Date(s): Submitted: August 31, 2005
PDUFA: June 30, 2006

Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical Reviewer: Yongman Kim, Ph.D.

Concurring Reviewers: Thomas Permutt, Ph.D.

Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products

Clinical Team: Robert Shibuya, M.D.

Project Manager: Kimberly Compton

Keywords: ANOVA, cross-over design, permutation test

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study 099-14 with opioid-tolerant cancer patients provided data showing efficacy of ORAVESCENT fentanyl (OVF) citrate for use in the management of breakthrough pain (BTP) based on modified intent-to-treat (mITT) analysis. In terms of the summed pain intensity difference (SPID) at 30 minutes, ORAVESCENT fentanyl citrate was shown as superior to the placebo. (See Tables 3 - 5.)

Overall, the submitted data provide statistically significant results (OVF $SPID_{30} = 3.0$ vs. placebo $SPID_{30} = 1.8$; $p<.0001$) supporting analgesic efficacy of ORAVESCENT fentanyl citrate buccal tablet in treating cancer-related BTP.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of one phase III efficacy study 099-14. It was agreed between the sponsor and FDA that at least one adequate and well controlled study is required for approval as 505(b) (2) application.

The design for the study was a double-blind, randomized, placebo-controlled, multi-center, crossover trial to investigate the safety and analgesic effect of ORAVESCENT fentanyl citrate in opioid-tolerant cancer patients. Seventy-seven patients were randomized to one of eighteen possible sequences with ten treatment periods. There were seven periods of ORAVESCENT fentanyl citrate and three periods of matching placebo, with restrictions: the first period should be treated with ORAVESCENT fentanyl citrate and a placebo should be given in the second or third period; the next placebo between the fourth and sixth period; the last placebo after the sixth period; and placebo periods should not be adjacent.

The primary objective was to demonstrate the superiority in analgesic efficacy of ORAVESCENT fentanyl citrate buccal tablet compared to placebo.

The primary efficacy endpoint was the summed pain intensity difference at 30 minutes. Secondary efficacy endpoints were pain relief, global medication performance assessment, rescue medication usage, and time to rescue medication.

1.3 Statistical Issues and Findings

A permutation test on the primary comparison was recommended by Dr. Permutt to the sponsor after his review of the statistical analysis plan due to the possibility of confounding with an unbalanced randomization scheme. (See Statistical Review – IND Protocol Clinical Studies documented via DFS on March 7, 2005 under IND 65,447/N-

030-IM.) The sponsor conducted the permutation test confirming their primary comparison based on ANOVA.

I re-analyzed the primary variable using ANOVA with sequence and period terms in addition to treatment, site, and subject term as proposed by the sponsor.

To check if there was any systematic departure from random assignment of sequence to the patients with probability 1/18, I conducted a chi-square test. The test did not show a statistical departure from randomness ($p = .114$). This was done because the protocol was not clear about the randomization algorithm. However, the significance test result should be taken with caution due to possibility of low power of the test.

In their primary analysis, the sponsor used the analysis set of 'as-treated' population due to 15 patients' non-adherence to the assigned sequence of study drug. The sponsor and I conducted a sensitivity analysis with modified intention-to-treat as pre-defined and confirmed that the results led to the same conclusion.

Based on my review of the data, I obtained the following findings.

Data from Study 099-14 showed the superiority of ORAVESCENT fentanyl citrate when compared to placebo in terms of the summed pain intensity difference at 30 minutes by both sponsor and me.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

The following are quotes from the submission regarding drug class.

> The rapid onset of analgesia needed for effective management of BPT has been achieved by oral transmucosal delivery of potent, synthetic opioid fentanyl (a μ–receptor agonist). ACTIQ® (oral transmucosal fentanyl citrate) is the only medication approved in USA by the FDA for the management of BTP in opioid-tolerant patients with cancer.
>
> ORAVESCENT® fentanyl citrate has been developed as an alternative system for the transmucosal delivery of fentanyl and is in Phase 3 of clinical development for the management of BTP in opioid-tolerant patients with cancer and BTP. ORAVESCENT® fentanyl is a tablet that is placed buccal between the upper gum and the mucosal surface of the cheek above a molar tooth. The delivery of fentanyl from this formulation is passive, whereas ACTIQ requires the patient to actively maneuver the lozenge against buccal surface of the mouth. The ORAVESCENT fentanyl tablet contains a dose of fentanyl (100, 200, 400, 600, or 800 mcg of

fentanyl base) and components that enhance the dissolution of the tablet and absorption of fentanyl across the oral mucosa.

The following are excerpts from the submission regarding regulatory history and interactions between the sponsor and FDA prior to NDA.

During the pre-IND meeting with the Reviewing Division on November 1, 2001, after explaining its proposed drug development plan to the Agency, the sponsor and Agency representatives agreed that at least one adequate and well-controlled efficacy study is required to support an NDA for the proposed indication. During the December 5, 2003 End of Phase 2 meeting, the Agency agreed that the proposed Study 099-14 would adequately support the registration of OraVescent fentanyl as a single pivotal study. During the April 6, 2005 Pre-NDA meeting, the Agency requested the sponsor to provide information to specifically address which information is being referenced and what portions of the NDA is referenced if 505(b)(2) application is submitted.

To satisfy the Agency's requests, the sponsor agreed to conduct a Phase 3 clinical trial, Study 099-14. The study has now been completed and data from the study are included in this 505(b)(2) application.

2.1.2 Proposed Indication for ORAVESCENT® fentanyl citrate

2.2 Data Sources

The study report and electronic SAS data submission on August 31, 2005 can be found on the FDA, CDER electronic document room (EDR).

Study report:

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Data set:

\\Cdsesub1\n21947\N_000\2005-08-31\crt\datasets\Study 099-14

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The design for the study 099-14 was a multicenter, randomized, double-blind, placebo-controlled, 10-period crossover. After a titration period, patients were given ten numbered doses to be used for ten separate episodes of breakthrough pain. Seven of the ten doses were the active investigational drug and three were placebo. Which three doses were placebo was determined at random. However, the randomization was subject to several restrictions. The first dose was always active. Either dose 2 or 3 was placebo, at random. Either dose 4, 5 or 6 was placebo, and likewise 7, 8, 9 or 10; but placebo doses could not be consecutive. Even though randomization algorithm was not clear in the study protocol, the study report clarified that the eighteen possible treatment sequences satisfying the restrictions were randomly assigned to each patient.

Figure 1 in Appendix shows schematic of design for the study.

Thirty investigators enrolled subjects from US sites and participated in the clinical trial.

Seventy-seven subjects achieved successful dose during titration and were randomized to one of eighteen sequences with ten treatment periods.

The primary objective of the study was to demonstrate the superiority in analgesic efficacy of ORAVESCENT fentanyl citrate as compared to placebo.

The primary efficacy endpoint was $SPID_{30}$, the summed pain intensity difference (SPID) 30 minutes after the start of study drug, defined as $SPID_{30} = PID_{15} + PID_{30}$, where $PID_i = PI_0 - PI_i$ and PI was ranged from 0 ("no pain") to 10 ("worst pain").

The secondary efficacy endpoints were SPID at 45 and 60 minutes, PID, Pain Relief (PR) scores (0 = "none", 1 = "slight", 2 = "moderate", 3 = "lots", 4 = "complete"), Total Pain Relief (TOTPAR), global medication performance assessment (0 = "poor", 1 = "fair", 2 = "good", 3 = "very good", 4 = "excellent"), rate of rescue medication usage, and time to use of rescue medication. TOTPAR was derived as a cumulated sum over time from PR scores.

3.1.2 Patient Disposition and Demographics

As shown in Table 1 in Appendix, 123 out of 139 screened patients were enrolled and 77 were randomized to the double-blind treatment after titration. Sixty-eight patients completed the double-blind treatment periods.

Table 2 in Appendix shows patient demographics for Studies 099-14.

3.1.3 Statistical Methodologies

ANOVA model with terms for treatment and site as fixed effects and subject nested in site as random effect was used to compare SPID between treatment groups by the sponsor. I reanalyzed the efficacy variable by including sequence and period terms in addition to treatment, site and subject terms in the ANOVA model to assess the treatment effect after adjusting for potential imbalance in sequence and period due to restricted randomization. For the secondary efficacy variables such as PID, PR, and global medication performance assessment (GMPA), one-sample Wilcoxon signed rank test was used and for incidence of rescue medication use, CI interval for relative risk ratio was calculated.

Primary efficacy analysis population was modified intention-to-treat (mITT) set defined as all randomized patients who received at least one doses of ORAVESCENT fentanyl citrate and placebo, and had at least one pre-treatment pain intensity score for each of these episodes. I think that this analysis set was acceptable because an exclusion of patients with only episode(s) of one treatment could lead to less bias in this crossover design study than in parallel design study.

Missing values of PI in SPID calculation in a BTP episode were imputed by the last observation carried forward. Missing SPID scores for BTP episodes after dropout were not imputed at all and were excluded from the analysis.

3.1.4 Results and Conclusions

Following is a summary of results.

Data from the study showed the superiority of ORAVESCENT fentanyl citrate over placebo in terms of the primary efficacy variable, SPID, in both the sponsor's analysis and my sensitivity analyses with respect to analysis set and ANOVA terms (all p-values <.001). (See Tables 3 – 5.)

Table 1. Sponsor Analysis of Primary Efficacy Variable for Study 099-14: $SPID_{30}$ (Full Analysis Population)

$SPID_{30}$	OVF (N=72)	Placebo (N=72)	p-value
LSMEAN (SE)	3.0 (.12)	1.8 (.18)	<.0001*
PERMUTATION TEST			<.0004**

Note: Treatment group was defined as 'as-treated' for each episode.
* P-value based on ANOVA with terms for treatment, site as fixed effects and subject as random effect.
** P-value of permutation test based on 10,000 re-randomizations.

Table 2. Reviewer Analysis of Primary Efficacy Variable for Study 099-14: $SPID_{30}$ (mITT Population)

$SPID_{30}$	OVF (N=72)	Placebo (N=72)	p-value*
LSMEAN (SE)	3.1 (.31)	1.8 (.35)	<.0001

Note: Treatment group was defined as 'as-randomized' for each episode.
* P-value based on ANOVA with terms for treatment, site as fixed effects and subject as random effect.

Table 3. Reviewer Analysis of Primary Efficacy Variable for Study 099-14: $SPID_{30}$ (mITT Population)

$SPID_{30}$	OVF (N=72)	Placebo (N=72)	p-value*
LSMEAN (SE)	2.9 (.35)	1.7 (.37)	<.0001

Note: Treatment group was defined as 'as-randomized' for each episode.
* P-value based on ANOVA with terms for treatment, site, sequence, period as fixed effects and subject as random effect.

There were statistically significant differences between treatment groups in terms of the secondary variables such as TOTPAR, GMPA, and incidence of rescue medication in the sponsor analyses. (See Tables 7 – 9 in Appendix.)

3.2 Evaluation of Safety

Safety analyses were done by Clinical reviewer, Robert Shibuya, M.D.

No statistical problems or issues were found.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analyses were planned or conducted by the sponsor. I conducted following subgroup analyses: gender group (male, female), age group (<65, >65; >75).
There was no statistically significant interaction either between sex and treatment (p=.1447) or age group (<65, >65) and treatment (p=.1202). There were 7 patients who were older than 75. For this patient group, there was no statistically significant difference between treatment groups ($SPID_{30}$ for OVF = 3.6 and $SPID_{30}$ for placebo = 3.7; p=.9348).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

A permutation test on the primary comparison was recommended by Dr. Permutt to the sponsor after his review of the statistical analysis plan due to the possibility of confounding with an unbalanced randomization scheme. (See Statistical Review – IND Protocol Clinical Studies documented via DFS on March 7, 2005 under IND 65,447/N-030-IM.) The sponsor conducted the permutation test confirming their primary comparison based on ANOVA.

I re-analyzed the primary variable using ANOVA with sequence and period terms in addition to treatment, site, and subject term as proposed by the sponsor.

To check if there was any systematic departure from random assignment of sequence to the patients with probability 1/18, I conducted a chi-square test. The test did not show a statistical departure from randomness ($p = .114$). This was done because the protocol was not clear about the randomization algorithm. However, the significance test result should be taken with caution due to possibility of low power of the test.

In their primary analysis, the sponsor used the analysis set of 'as-treated' population due to 15 patients' non-adherence to the assigned sequence of study drug. The sponsor and I conducted a sensitivity analysis with modified intention-to-treat as pre-defined and confirmed that the results led to the same conclusion.

5.1.2 Collective Evidence

The data from the study 099-14 for analgesic efficacy provided statistically significant evidence of efficacy of ORAVESCENT fentanyl citrate as a treatment of BTP in cancer patients. The efficacy study met our standards for analgesic indication and agreement between the sponsor and FDA during regulatory interactions.

5.2 Conclusions and Recommendations

Study 099-14 with opioid-tolerant cancer patients provided data showing efficacy of ORAVESCENT fentanyl citrate for use in the management of BTP based on mITT analysis. In terms of the summed pain intensity difference at 30 minutes, ORAVESCENT fentanyl citrate was shown as superior to the placebo.

Overall, the submitted data provide statistically significant results (OVF $SPID_{30} = 3.0$ vs. placebo $SPID_{30} = 1.8$; $p<.0001$) supporting analgesic efficacy of ORAVESCENT fentanyl citrate buccal tablet in treating cancer-related BTP.

5.3 Review of Clinical Studies of Proposed Label

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

APPENDIX

Table 4. Patient Disposition

Study 099-14:

	NUMBER (%) OF PATIENTS
SCREENED:	139
ENROLLED:	123 (100)
RANDOMIZED:	77 (63)
mITT:	72 (59)
COMPLETED:	68 (55)
DISCONTINUED:	9 (7)
Adverse events	3 (2)
Lack of efficacy	0 (0)
Other	6 (5)

Table 5. Patient Demographics (All Randomized Subjects)

Study 099-14:

	N (%)
Gender	
Male	67 (54)
Female	56 (46)
Race	
White	109 (88)
Black	2 (2)
Other	12 (10)
Age (years)	
Mean ± SD	58.0 ± 12.6
Range	27 - 87
Weight (kg)	
Mean ± SD	74.7 ± 18.5
Range	39.5 – 147.2

Table 6. Sponsor Analysis of Secondary Efficacy Variable for Study 099-14: SPID (Full Analysis Population)

	OVF (N=72)	Placebo (N=72)	p-value*
$SPID_{15}$ **LSMean (SE)**	.8 (.06)	.5 (.08)	.0005
$SPID_{45}$ **LSMean (SE)**	6.3 (.20)	3.6 (.30)	<.0001
$SPID_{60}$ **LSMean (SE)**	10.2 (.30)	5.8 (.44)	<.0001

Note: Treatment group was defined as 'as-treated' for each episode.
* P-values based on ANOVA with terms for treatment, site as fixed effects and subject as random effect.

Table 7. Sponsor Analysis of Secondary Efficacy Variable for Study 099-14: TOTPAR (Full Analysis Population)

	OVF (N=72)	Placebo (N=72)	p-value*
$TOTPAR_{15}$ **LSMean (SE)**	.7 (.03)	.5 (.05)	.0001
$TOTPAR_{30}$ **LSMean (SE)**	2.1 (.07)	1.3 (.10)	<.0001
$TOTPAR_{45}$ **LSMean (SE)**	3.9 (.11)	2.4 (.17)	<.0001
$TOTPAR_{60}$ **LSMean (SE)**	6.0 (.17)	3.8 (.25)	<.0001

Note: Treatment group was defined as 'as-treated' for each episode.
* P-values based on ANOVA with terms for treatment, site as fixed effects and subject as random effect.

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Table 8. Sponsor Analysis of Secondary Efficacy Variable for Study 099-14: Global Medication Performance Assessment (GMPA) (Full Analysis Population)

	OVF (N=72)	Placebo (N=72)	p-value*
GMPA AT 30 MIN. Mean (SD)	1.4 (.84)	.9 (.91)	<.0001
GMPA AT 30 MIN. Mean (SD)	2.1 (.81)	1.3 (1.06)	<.0001

Note: Treatment group was defined as 'as-treated' for each episode.
* P-values based on one-sample Wilcoxon signed rank test.

Table 9. Sponsor Analysis of Secondary Efficacy Variable for Study 099-14: Incidence of Rescue Medication Use (Full Analysis Population)

	OVF (N=72)	Placebo (N=72)	relative risk ratio (95% CI)
NO. OF BTP	493	208	
No. of Rescue Medication Use (%)	117 (23%)	105 (50%)	.47 (.37, .60)

Note: Treatment group was defined as 'as-treated' for each episode.
* 95% CI based on the formula:
.47xexp[-1.96xsqrt{(1-117/493)/117+(1-105/208)/105}],
.47xexp[1.96xsqrt{(1-117/493)/117+(1-105/208)/105}].

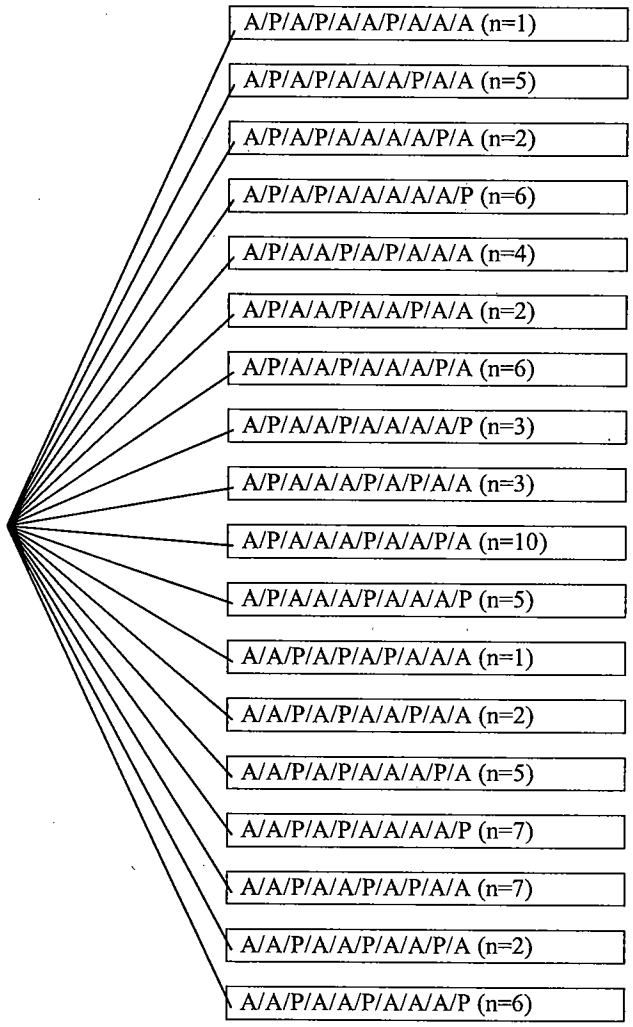
Figure 1. Schematic of Study Design

Study 099-14:

(N=77)

Randomized to

One of 18 sequences



SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.
Mathematical Statistician

Date: May 2, 2006

Concurring Reviewer: Thomas Permutt, Ph.D.
Statistical Team Leader

cc:

DAARP/Kimberly Compton
DAARP/Robert Shibuya, M.D.
HFD-715/Yongman Kim, Ph.D.
HFD-715/Thomas Permutt, Ph.D.
HFD-715/Edward Nevius, Ph.D.
HFD-715/Steve Wilson, Ph.D.
HFD-700/Lillian Patrician
HFD-700/Robert O'Neil, Ph.D.

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