CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022569Orig1s000

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

RESPONSE TO DIVISION OF SCIENTIFIC INVESTIGATIONS REPORT

NDA/Serial Number:	22-569/0000
Drug Name:	Fentanyl Citrate Nasal Spray
Indication(s):	Treatment of breakthrough cancer pain
Applicant:	Archimedes Development Limited
Date(s):	Received: August 31, 2009
	PDUFA: June 30, 2010
Review Priority:	Standard – 10 month
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	David Petullo, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia and Analgesia Products
Clinical Team:	Medical Officer: Luke Yip, M.D.
	Medical Team Leader: Robert Shibuya, M.D.
Project Manager:	

Keywords: NDA review

1. Clinical Inspection Summary

The Division of Scientific Investigations (DSI) conducted an inspection of two sites based on enrollment size and number of protocol violations. The sites are shown in Table 1.

Table 1. Sites inspected by Division of Scientific Inspections

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates
Mark R Wallace, M.D. UCSD Clinical Trials Center 9310 Campus Pt. Drive Mod A, Rm 117 UCSD Clinical Trials Center La Jolla, CA 92037 United States Phone#: 602-252-6855 Fax#: 602-252-2223 E-Mail: markw@samaritan.edu	CP043/06/FCNS/ 10/	17 Dec 09-11 Jan 10
Vincent Galan, M.D. SRMC Pain Clinic 11 Upper Riverdale Rd. SW Riverdale, GA 30274 United States Phone#: 770-991-2289 Fax#: 954-323-4094 E-Mail: vgalan@msn.com	CP043/06/FCNS/ 15/	11-21 Jan 2010

Source: DSI memorandum

DSI recommended removing one patient, subject 08, from Dr. Wallace's site and three patients, subjects 102, 109, and 113, from Dr. Galan's site. The rationale for removing subject 08 from Dr. Wallace's site was a discrepancy in the number of doses received. However when I examined the electronic case report forms, this patient was a screening failure and did not receive study drug. This discrepancy was conveyed to DSI. The rational for removing the patients from Dr. Galan's site was missing information on use of concomitant medications. For completeness, I reanalyzed the primary endpoint, summed pain intensity difference 30 minutes after dosing, excluding subjects 102, 109, and 113. Subject 08 was not included in my original analysis. There was still a significant treatment effect observed when these data were removed from the analysis. The DSI report does not change my conclusion; there is statistical evidence of the efficacy of Fentanyl Citrate Nasal Spray in treating episodes of breakthrough cancer pain in subjects on regular opioid therapy.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

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concur

U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Keywords: Clinical trials, NDA review, crossover design

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Archimedes Development Limited has submitted an application evaluating Fentanyl Citrate Nasal Spray (FCNS) for the treatment of breakthrough cancer pain (BTCP). Based on my review of the data from one controlled clinical trial, Study CP043/06/FCNS (CP043), I conclude there is statistical evidence of the efficacy of FCNS in treating episodes of BTCP in subjects on regular opioid therapy. For this study, the predefined primary endpoint, summed pain intensity difference 30 minutes after dosing ($SPID_{30}$), was statistically significantly in favor of FCNS. The conclusions were supported by the analyses of secondary endpoints such as pain intensity difference from baseline (PID), pain relief (PR) scores, and use of rescue medication.

1.2 Brief Overview of Clinical Studies

The Applicant submitted two randomized trials to support efficacy; one placebo-controlled (Study CP043) and one active-controlled (Study CP044/06/FCNS). Since the reviewing medical officer deemed that the active-controlled study used the inappropriate endpoint, this study was not reviewed. My review is based on a randomized, multicenter, placebo-controlled, double-blind, two-phase, crossover clinical trial. This study treated episodes of BTCP in patients on chronic opioids. Cancer patients who experienced on average one to four episodes of BTCP while taking at least 60 mg of morphine (or equivalent) for the underlying cancer pain were enrolled at centers in the United States, Costa Rica, and Argentina. Patients initially entered an open-label titration phase to determine an effective dose of FCNS. Those that achieved an effective dose entered a randomized, double-blind, placebo-controlled, crossover phase where up to 10 episodes of BTCP were treated with placebo or FCNS. Given a patient had at least one episode treated with placebo and one episode treated with FCNS, the primary endpoint, $SPID_{30,}$ was analyzed using a mixed effects model with treatment and center as fixed effects and subject as a random effect. Secondary endpoints examined by the Applicant included pain intensity (PI) scores, PID, PR scores, total pain relief (TOTPAR), proportion of patients with at least a 2-point reduction in baseline pain, use of rescue medication, and subject acceptability assessments.

1.3 Statistical Issues and Findings

During my review I had several concerns regarding the Applicant's analysis population. The modified intent-to-treat (mITT) population was defined as all randomized patients that had at least one evaluable placebo-treated episode and at least one FNCS-treated episode. An evaluable episode was defined as an episode that was treated with study drug, had a baseline pain score, had at least one post-treatment pain score, and was the only episode associated with a single canister. The mITT population should not have excluded episodes that lacked pre- or post-treatment pain assessments. Any patient who was randomized and received both placebo and study drug should have been included in the analyses. While the Applicant excluded 10 patients from the mITT population, I only excluded three patients from my analyses. The Applicant also classified 49 episodes from 14 additional patients as not evaluable. After evaluating each episode separately, I decided to include 27 of these episodes in my analyses datasets. Further, there were 12 patients that had episodes analyzed "as treated" rather than "as randomized", i.e. canisters were used out of sequence. My primary analysis evaluated these patients "as randomized". However, regardless of these concerns, my results confirmed the

Applicant's conclusion. There was a statistically significant treatment effect observed in favor of FNCS when treating episodes of BTCP.

2. INTRODUCTION

2.1 Overview

FNCS is a formulation of fentanyl and pectin intended to treat episodes of BTCP using a nasal delivery system. The Applicant claims that when compared to other oral fentanyl products, FNCS is absorbed more rapidly, to a greater extent, and with a pharmacokinetic profile more suited to treat the duration of BTCP episodes. The development plan for FNCS was discussed with the Agency at various meetings from 2005–2008 under IND 70,854. A pre-IND meeting was held on April 26, 2005, an end of phase 2 (EOP2) meeting on August 22, 2006, and a pre-NDA meeting on Sept 22, 2008. The Agency agreed that one positive, adequate and well-controlled trial would support a 505 (b)(2) application. During the EOP2 meeting, the statistical reviewer requested detailed information regarding the statistical analysis. Specific information was requested regarding the treatment sequences assigned at randomization and imputation methods for missing data. There was also a comment about the crossover design; the statistical methodology should account for dependent observations between subjects.

2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

\\cdsesub1\evsprod\NDA022569\0000\m5\datasets\cp043

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study CP043/06 was conducted from December 2006 to July 2008 at 58 centers in the United States, Costa Rica, and Argentina. The majority of patients randomized to treatment were from the United States; 6 patients from Costa Rica and 74 from the United States. Of the five patients screened in Argentina, none were randomized.

The statistical analysis plan for this protocol was reviewed by me in May, 2008. The main concern noted was the Applicant's definition of the mITT population. It should not have excluded patients that were randomized and received treatment but failed to record post-treatment pain score. I also commented on missing baseline scores; a baseline pain score should not be missing as it was the main criteria for an episode to be treated. There was no response from the Applicant regarding these concerns.

3.1.1 Study Design and Endpoints

Patients that were able to achieve an effective dose of FNCS entered a randomized, double-blind, placebo-controlled phase where they were to treat up to 10 episodes of BTCP. Patients were randomized to 1 of 10 unique sequences as shown in Table 1.

Table 1. Treatment sequences assigned at randomization.

Sequence Key: P=Placebo; N=Nasalfent

Sequence Letter	Sequence of Treatments
A	N P N P N N P N N N
B	N N P N P N N N P N
C	N N P N N P N P N N
D	P N N N P N N N N P
E	P N N N P N N N P N
F	N N P N N P N N N P
G	N P N N N N P N P N
H	N N N P N N P N N P
I	P N N N N P N P N N
J	N P N P N N N P N N

Source: Page 10 of Applicants SAP
Note: N=Nasalfent=FCNS

The Applicant claimed these 10 sequences were chosen randomly from all possible sequences excluding those with 2 consecutive placebo doses. However, it did not seem completely at random as there were exactly 3 placebo doses for each episode (columns). While this is good, the study should also be balanced across rows to account for any potential effect of carryover. Although the Applicant did not account for carryover in their analysis, the study did specify that there should be at least four hours between each treated episode. Since the half-life of fentanyl is approximately 45 minutes, four hours should be sufficient time to eliminate any carryover effect. However, for thoroughness, I included a period effect in my analysis of the primary endpoint, see section 3.1.4.

The primary measure of efficacy was pre-specified as the comparison of $SPID_{30}$. SPID was defined as the cumulative sum of the recorded PID scores. Secondary measures included PI scores, PID, PR scores, total pain relief (TOTPAR), and patient acceptability scores at 30 and 60 minutes post-dose. PI and PR scores were measured at 5, 10, 15, 30, 45, and 60 minutes post-dose. PI was measured using an 11-point scale with 0 being no pain and 10 the worst possible pain. PR was measured using a 5-point scale with 0 being no relief and 4 being complete relief. Patient's acceptability assessments measured overall satisfaction, ease of use, and convenience using a 4-point scale: 1=not satisfied; 2=not satisfied or dissatisfied; 3=satisfied; 4=very satisfied. TOTPAR was defined as the sum of PR scores over a specified time period.

Based on the results of an approved application (Actiq, NDA 21-747), the Applicant used a treatment effect of 2.25 and a standard deviation of 4.35 for $SPID_{30}$ to estimate that 80 patients would provide 90% power to detect a treatment difference if there truly was a treatment effect.

3.1.2 Patient Disposition and Demographics

The study screened 139 patients. Of these, 114 entered the titration phase and 83 patients were successfully titrated and entered the randomized double-blind treatment phase. Seventy-six patients completed the study. Demographics for the randomized patients are shown in Table 2.

Table 2. Demographics for patients randomized

Characteristic	
Number of Patients (n)	83
Age in years	
Mean (SD)	53(12)
Median	53
[range]	[21, 86]
Gender (%)	
Female	36 (43)
Male	47 (57)
Race (%)	
Caucasian	59 (71)
Black	8 (10)
Southeast Asian	2 (2)
Other: Hispanic	14 (17)

Source: Reviewer

There were seven randomized patients that discontinued treatment prematurely. The reasons for discontinuation are shown in Table 3.

Table 3. Disposition of patients that discontinued

Reason for Discontinuation	n
Death	1
Adverse event	1
Withdrew consent	3
Lack of Efficacy	1
Lost-to-follow up	1

Source: Reviewer

3.1.3 Statistical Methodologies

The primary efficacy endpoint was pre-defined as $SPID_{30}$. Results for placebo-treated episodes were compared to FNCS-treated episodes using a mixed effects model with treatment and center as fixed effects and subject was included as a random effect. Since enrollment at each center was low, centers were pooled to have approximately 20 subjects at each center. The Applicant examined a treatment interaction with center, age, sequence, and an indicator of rescue use.

Analyses of secondary endpoints were conducted to provide additional support for efficacy. Secondary endpoints examined in my review included PID and PR scores at each measured time point, TOTPAR, proportion of patients achieving at least at least a two-point improvement in baseline pain, and use of rescue medication. Mean scores for PID and PR were compared at each measured time point using the same mixed effects model listed above. I examined rescue medication use for each episode as taken or not taken (binary response) and analyzed the results using a generalized linear mixed effects model with treatment and center as fixed effects and subject as a random effect.

The Applicant used last observation carried forward (LOCF) to impute values due to omission or use of rescue medication. I did not agree with this approach for patients that used rescue medication. To be conservative, I used baseline observation carried forward (BOCF) for patients that used rescue medication and LOCF for intermittent missing data.

The Applicant's mITT population excluded 10 patients from the ITT population. A justification for the exclusion of each patient is given in Table 4.

Table 4. Applicant's justification for excluding patients from the mITT population

Patient Number	Primary Reason for Exclusion	Details
910/391005	Only Nasalfent data	2 episodes (Nasalfent), only 1 was evaluable
913/391304	No evaluable data	20 episodes (Nasalfent and placebo), all bottles had been used more than once
931/393101	Only Nasalfent data	2 episodes (Nasalfent and placebo) but only Nasalfent episode was evaluable
940/394003	Lost to follow-up	Medication dispensed, but patient failed to return and supplied no e-diary data
941/394107	No evaluable data	Episodes were recorded in the e-diary, but bottle numbers were missing
941/394109	Only Placebo data	8 episodes (Nasalfent and placebo). The 1 Nasalfent evaluable episode was excluded because the bottle was used more than once
945/394501	No evaluable data	Episodes were recorded in the e-diary, but bottle numbers were missing
980/398001	Only Nasalfent data	3 episodes (Nasalfent and placebo), but only 2 Nasalfent episodes were evaluable; placebo episode was not evaluable
980/398005	Only Nasalfent data	3 episodes (Nasalfent and placebo), but only 1 Nasalfent episode evaluable
980/398006	Only Nasalfent data	24 episodes (Nasalfent and placebo), but only 1 Nasalfent bottle used once, all others were used more than once

Source: Table 5 from the Applicant's study report

I examined each excluded patient and decided to include seven of them in my analysis population. I determined that missing a pre- or post-treatment pain assessment was not a valid reason to exclude a patient from the mITT population. The applicant also excluded a patient if all canisters were used more than once. I included the first episode treated with a single canister and excluded any additional episodes treated with the same canister and analyzed data "as randomized". These patients and my remedial action are shown in Table 5.

Table 5. Patients excluded from the Applicant's mITT population but included in Reviewer's

Patient number	Remedial action
391304	Since the first 10 episodes were treated in the correct sequence, they will be included in the analysis, the second 10 will not.
393101	Include placebo episode and impute SPID30=0 since baseline score was missing.
394107	Included first 10 treated episodes and analyze according to randomization.
394109	Include FNCS episodes 1, 2, 4, 7, and 8 (impute SPID30=0 since no PI scores were available). Exclude second use of canister 1.
394501	Include episodes and analyze episodes according to randomization.
398005	Include placebo episodes and impute SPID30=0 since baseline score was missing.
398006	Include the 7 episodes that were treated with single canister, episodes 3, 4, 5, 6, 7, 23, and 26 and analyze as randomized.

Source: Reviewer

I do not agree with the Applicant's definition of "evaluable"; defined as an episode that was treated with study drug, had a baseline pain score, had at least one post-treatment pain score, and was the only episode associated with a single canister. There were 49 episodes from 14 patients in the Applicant's analyses deemed not evaluable. I examined each episode and decided to include 27 of them in my analyses. If an episode was missing a baseline or post-treatment pain, I imputed a score of PID=0.

3.1.4 Results

Primary Efficacy Endpoint

Since I did not agree with the Applicant's definition of the mITT population, I conducted the primary and secondary analyses using a revised mITT. I included 7 patients that were excluded and 27 episodes that the Applicant had deemed not evaluable. Since several patients used bottles out of sequence, my analyses were conducted using "as randomized" and "as treated", Table 6. For comparison, I also included the results of the Applicant's analysis.

Table 6. Results of the primary analysis for $SPID_{30}$

Source	Mean $SPID_{30}$ (stdev)			
	Placebo	Fentanyl	Difference	p-value
Applicant, n=73	4.5 (5.5)	6.6 (5.0)	2.1	<0.001
As treated, n=80	4.6 (6.4)	6.0 (6.1)	1.4	<0.001
As randomized, n=80	4.7 (6.2)	6.0 (6.2)	1.3	<0.001

Source: Reviewer

The Applicant defined $SPID_{30}$ as the sum of the PID scores at 5, 10, 15, and 30 minutes post-dose. While this is acceptable, I examined a time weighted $SPID_{30}$ where each PID score is adjusted for the time interval between measurements. I used the mixed effects model described in section 3.1.2 to analyze data "as randomized" and "as treated", Table 7.

Table 7. Results of analysis for time-weighted $SPID_{30}$

Source	Mean time-weighted$SPID_{30}$ (stdev), PID*hr			
	Placebo	Fentanyl	Difference	p-value
As treated, n=80	2.7 (3.6)	3.7 (3.4)	1.0	<0.001
As randomized, n=80	2.7 (3.5)	3.7 (3.4)	1.0	<0.001

Source: Reviewer

Since this was a crossover study, I also examined the primary endpoint for the potential effect of sequence and period by including them in the analysis. The results did not change. There was still a significant treatment effect.

Secondary Efficacy Endpoints

As further supportive evidence of efficacy, I examined PID and PR scores at each assessed time point. These endpoints are supportive in nature and will not be included as label claims. The Applicant did not account for multiplicity. However, the endpoints are highly correlated, thus multiplicity is probably less of a concern. I used my mITT population and imputation methods, BOCF for patients who used rescue medication and LOCF for intermittent missing data for these analyses. Data were analyzed "as randomized" and "as treated" using the mixed effects model as described for the primary endpoint. Results are shown in Table 8.

Table 8. Mean PID values by time

Minutes post-treatment	Mean PID (n=80)			
	As treated		As Randomized	
	Placebo	Fentanyl	Placebo	Fentanyl
5	0.5	0.6	0.5	0.5
10	1.0	1.2*	1.0	1.2*
15	1.4	1.8**	1.4	1.8**
30	1.8	2.5**	1.8	2.5**
45	2.1	3.1**	2.1	3.1**
60	2.2	3.4**	2.3	3.4**

Source: Reviewer

* p-value < 0.05, ** p-value < 0.001

Episodes treated with FNCS had a larger mean PID than episodes treated with placebo at all measured time points. There was statistical significance in favor of FNCS at 10, 15, 30, 45, and 60 minutes post-treatment.

I also examined the proportion of episodes where PID showed at least a 2-point improvement from baseline. Data were analyzed using a generalized linear mixed effects model with treatment and center as fixed effects and subject as a random effect. Results are shown in Table 9.

Table 9. Proportion of patients achieving at least 2 point reduction in baseline pain

Minutes post-treatment	Proportion achieving ≥ 2 PID (n=80)			
	As treated		As Randomized	
	Placebo	Fentanyl	Placebo	Fentanyl
5	11	13	12	12
10	25	31	25	31
15	33	48*	33	48*
30	42	63**	43	63**
45	47	70**	48	69**
60	50	74**	50	74**

Source: Reviewer
* p-value < 0.05, ** p-value < 0.001

Consistent with what was observed with PID scores, after 5 minutes post dose, a larger proportion of FNCS-treated episodes had at least a 2-point improvement in baseline pain than placebo-treated episodes. Statistical significance was observed at 15-60 minutes post-treatment.

PR scores were also examined at each measured time point. Missing data was handled by using LOCF for intermittent missing data and using a score of zero, i.e. no pain relief, for all other missing data and for scores after use of rescue medication. Results for placebo and FNCS were compared using a mixed effects model with treatment and pooled center as fixed effects and subject as a random effect. Results are shown in Table 10.

Table 10. Mean PR scores by time

Minutes post-treatment	Mean pain relief scores (n=80)			
	As treated		As Randomized	
	Placebo	Fentanyl	Placebo	Fentanyl
5	0.65	0.69	0.66	0.68
10	0.83	1.06*	0.84	1.05*
15	1.07	1.39*	1.07	1.39*
30	1.19	1.77*	1.21	1.77*
45	1.29	1.96*	1.29	1.96*
60	1.32	2.01*	1.32	2.01*

Source: Reviewer
* p-value < 0.001

There was a significant treatment effect observed at 10-60 minutes post-dose in favor of FNCS. Note, for PID and PR scores, comparisons were made at each time point without adjusting for multiplicity. I also examined TOTPAR scores at 30 post-treatment ($TOTPAR_{30}$). Data was analyzed using "as randomized" and "as treated" using the same mixed effects model described above, Table 11.

Table 11. Mean TOTPAR scores at 30 minutes post-dose.

Source	Mean $TOPAR_{30}$ (n=80)	
	Placebo	Fentanyl
As treated	3.7	4.9*
As randomized	3.8	4.9*

Source: Reviewer
* p-value < 0.001

Results were again consistent. There was a treatment effect in favor of FNCS.

Rescue medication use was evaluated by the Applicant for a treatment effect. They examined the proportion of subjects who used rescue medication at each time interval. The non-parametric McNemar's test was used to make comparisons, Table 12.

Table 12. Applicant's analysis of rescue medication use

Treatment	**Number (%) of Patients Who Used Rescue Medication**					
(N=73)	**0-5 min**	**0-10 min**	**0-15 min**	**0-30 min**	**0-45 min**	**0-60 min**
Nasalfent	3 (4.1%)	4 (5.5%)	4 (5.5%)	6 (8.2%)	13 (17.8%)	26 (35.6%)
Placebo	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	12 (16.4%)	27 (37.0%)
P-values[1]	0.0833	0.0455	0.0455	0.1025	0.8084	0.8185

[1]P-values from McNemar Test to compare Nasalfent and placebo arms at each timepoint.
Source: Table 21 of the Applicant's Study Report

The Applicant's table seemed confusing. At 10, 15, and 30 minutes post-treatment, there were more patients who used rescue medication for FNCS-treated episodes and than for placebo-treated episodes. However, at 60 minutes post-dose, there were 26 patients who used rescue medication for FNCS-treated episodes and 27 for placebo. The Applicant also examined rescue use as a binary response. Each episode was classified as used rescue medication or did not use rescue medication. I repeated their analysis using my mITT population. There were 551 episodes of BTCP treated with FNCS of which 54 (10%) used rescue medication within one hour, and there were 235 BTCP episodes treated with placebo of which 42 (18%) used rescue medication. To compare use of rescue medication, I used a generalized linear mixed effects model with rescue use as the response variable, treatment and center included as fixed effects, and subject as a random effect. There was a significant treatment effect indicating that FNCS-treated episodes required significantly less rescue medication. My results are consistent with the Applicant's.

As I did not use the same analyses population or imputation methods as the Applicant, my results are slightly different. However, my conclusion does not differ from the Applicant's. The results of my analyses are in favor of FCNS. In general, patients reported less pain and greater pain relief during BTCP episodes treated with FCNS than those episodes treated with placebo.

3.2 Evaluation of Safety

The primary medical officer, Dr. Nick Olmos-Lau, reviewed the safety data for this NDA.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The Applicant examined age, gender, and race as a covariates in the analysis of $SPID_{30}$ to identify any possible treatment differences between subgroups. Age was considered as ≤ 60 years or > 60 years and race was classified as Caucasian or "all others". The Applicant reported the mean $SPID_{30}$ for treatment within each subgroup and in some cases made statistical comparisons, Table 13.

Table 13. Applicant's subgroup analysis for age, race, and gender for $SPID_{30}$

Subgroup	FNS Mean (SD)	Placebo Mean (SD)	Mean Effect Size
Age			
≤60 years (n=58)	6.59 (5.00)	4.34 (5.70)	2.25
>60 years (n=15)	6.50 (5.11)	4.89 (4.86)	1.69
Gender			
Female (n=35)	5.96 (4.46)	3.77 (4.93)	2.19
Male (n=38)	7.13 (5.42)	5.08 (5.99)	2.05
Race (all subgroups)			
Caucasian (n=53)	6.12 (4.29)	3.44 (4.37)	2.68
Black (n=7)	7.01 (8.70)	7.40 (9.59)	–0.39
SE Asian (n=2)	1.11 (0.56)	0.50 (0.71)	0.61
Other (n=11)	9.45 (4.66)	8.15 (5.88)	1.30
Race (dual subgroups)			
Caucasian (n=53)	6.12 (4.29)	3.44 (4.37)	2.68
All Others (n=20)	7.76 (6.47)	7.13 (7.25)	0.63

Post hoc statistical analyses	Parameter 1	Parameter 2	P-value for difference
Gender			
(Female, n=35)	Nasalfent (Female)	Nasalfent (Male)	0.3908
(Male, n=38)	Nasalfent (Female)	Placebo (Female)	0.0013
	NasalFent (Male)	Placebo (Male)	0.0017
	Placebo (Female)	Placebo (Male)	0.3045
Race			
(Caucasian, n=53)	Nasalfent (Caucasian)	Nasalfent (All Others)	0.2069
(All Others, n=20)	Nasalfent (Caucasian)	Placebo (Caucasian)	<0.0001
	NasalFent (All Others)	Placebo (All Others)	0.4552
	Placebo (Caucasian)	Placebo (All Others)	0.0090

Note: Comparisons between sub-groups by ANOVA mixed-effect model

Source: Table 10.1-1 from Applicant's ISE document

For race, there was only one subgroup, "all others", that lacked a significant treatment effect for the primary efficacy endpoint. To further explore the efficacy within subgroups, I examined the primary efficacy endpoint, $SPID_{30}$ for any treatment interactions with age, gender, or racial subgroups using my mITT population. I included a treatment interaction for age, gender, and racial subgroups in the mixed effects model used to analyze the primary efficacy variable, $SPID_{30}$. There was not a significant treatment interaction with age or gender, but I did note a significant interaction with racial subgroups. When I examined the comparisons within racial subgroups, the "all others" subgroup lacked a significant treatment effect. I attributed this finding to the lack of power to detect a difference in the subgroup.

4.2 Other Special/Subgroup Populations

While this study screened patients in the United States, Costa Rica, and Argentina, the majority of patients randomized to treatment were in the United States; 76 patients were randomized in the United States and 7 in Costa Rica. There were no patients from Argentina in the randomized phase of the study. Since my analyses population consisted of 6 patients from Costa Rica and 74 from the United States, I did not explore a treatment by country interaction. I simply summarized $SPID_{30}$ by country in Table 14.

Table 14. Mean SPID30 summarized by country

Subgroup	Mean $SPID_{30}$ (stdev)	
	Placebo	Fentanyl
Costa Rica, n=6	12.2 (8.3)	10.6 (7.8)
United States, n=74	4.1 (5.8)	5.7 (5.9)

Source: Reviewer

Although it appears that there is not a treatment effect in Costa Rica, this information is limited to the results of six patients

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I reviewed one clinical trial to support the efficacy of FNCS in treating patients experiencing episodes of BTCP. The Applicant reported a significant treatment effect for the primary endpoint, $SPID_{30}$. While I had concerns over the Applicant's definition of the mITT population used in their analyses, my concerns were alleviated when I was able to confirm the efficacy of FNCS using a revised mITT population. I also had a concern regarding how patients received treatment. Not all patients administered treatment according to the sequence assigned at randomization, i.e. bottles were not used in the correct order. To account for this, I analyzed data "as treated" and "as randomized". Regardless of the how the mITT population was defined or how data were analyzed, "as treated" or "as randomized", the primary efficacy endpoint, $SPID_{30}$ was significant in favor of FNCS. This was supported by various secondary endpoints.

5.2 Conclusions and Recommendations

Archimedes Development Limited has submitted an application seeking approval of FNCS in treating episodes of BTCP in opioid tolerant patients. Based on my review of a single

randomized, multicenter, placebo-controlled, double-blind, two-phase crossover clinical trial, I conclude that FNCS is superior to placebo in treating episodes of BTCP in cancer patients taking regular opioid therapy.

5.3 Label Review

Using the label provided in the submission, dated August 12, 2009, I had the following comments for Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized.

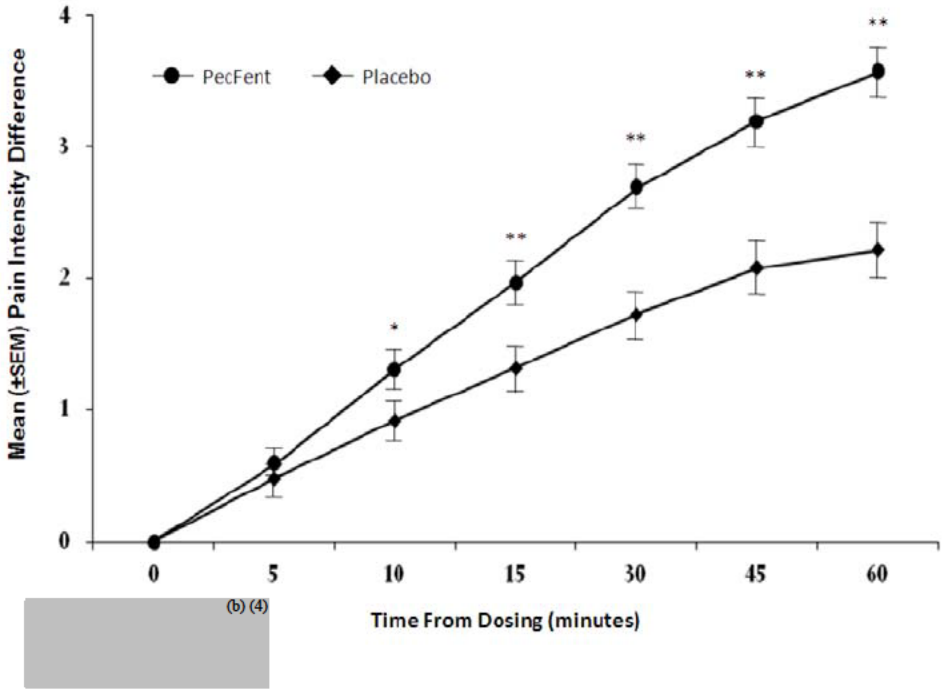
The above is consistent with the study report.

The above table should be revised to

(b) (4)

(b) (4)

Figure 2 – Mean Pain Intensity Difference (PID) at Each Time Point During the Double-Blind Treatment Period



(b) (4)

Since the primary endpoint, $SPID_{30}$ is derived from PID scores the inclusion of this graph is acceptable however, (b) (4) *This graph should be recreated using my mITT population.*

Using a reduction in pain intensity score of greater than or equal to 2 as a measure of clinically meaningful pain relief, the number of episodes showing a reduction was statistically significantly greater with PecFent versus with placebo at all time points from 10 to 60 minutes post-dose ($p=0.0110$ for 10 minutes; $p<0.0001$ for 15, 30, 45, and 60 minutes) (Figure 3).

There was a statistically significant difference in acceptability scores as measured on a 4-point scale between PecFent-treated episodes and those treated by placebo when assessed at both 30 and 60 minutes post dose ($p<0.0001$). Mean assessment scores for speed of relief and reliability also favored PecFent over placebo at both the 30- and 60-minute time points ($p<0.0001$); 68.5% of patients were "satisfied" or "very satisfied" that PecFent was easy to use.

The analyses of the secondary endpoints were not adjusted for multiplicity and there is no additional clinical information gleaned from these endpoints, they (b) (4)

In a double-blind, randomized ,comparator-controlled study (Study 044) of similar design to Study 043 conducted in opioid-tolerant patients with breakthrough cancer pain on stable doses of regularly scheduled opioids, PecFent was shown to be superior to immediate-release morphine sulfate (IRMS). Superiority was demonstrated by the primary endpoint, Pain Intensity Difference within 15 minutes, which was 3.02 in patients treated with PecFent compared to 2.69 in patients treated with IRMS ($p=0.0396$). Early onset of effect (as indicated by the percentage of episodes with a 1-point reduction) was significantly greater for PecFent than for IRMS in terms of both pain intensity and pain relief scores, within 5 minutes of dosing ($p=0.0326$ and $p=0.0034$, respectively). The number of episodes in which clinically meaningful pain relief was achieved, as measured by a reduction in pain intensity

(b) (4)

This study was not reviewed by the statistics team as it was an active controlled study that did not use the appropriate primary endpoint. (b) (4)

(b) (4)

This is an open-label study designed to provide information regarding the safety. It (b) (4)

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

DAVID M PETULLO
04/08/2010

DIONNE L PRICE
04/08/2010
Concur

STATISTICS FILING CHECKLIST FOR NDA 22-569

NDA Number: 22-569 **Applicant: Archimedes Development Ltd.** **Stamp Date: August 31 , 2009**

Drug Name: Fentanyl Citrate Nasal Spray **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF: **Study CPI-APA-304**

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		See comment 1
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comments:

1. A request was made for a subgroup analysis of gender, race, and age. The Applicant stated these analyses would submitted by Oct 20, 2009.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

DAVID M PETULLO
10/16/2009

DIONNE L PRICE
10/16/2009