CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

STATISTICAL REVIEW(S)

JUL 29 1998

Statistical Review and Evaluation

NDA 20-747/serial no. 037 (resubmission) Date of review:

By: Thomas Permutt

Name of drug: Actiq (oral transmucosal fentanyl citrate, OTFC)
Applicant: Anesta
Indication: pain
Documents reviewed: volumes 19.1, 19.8-11, 30 April 1998;
FAX submission 11 September 1997
Project manager: Ken Nolan
Medical reviewer: Charles Cortinovis, M.D.

Introduction

Actiq is the potent narcotic fentanyl in the form of a lozenge on a stick, intended to be dissolved in the mouth over about a quarter hour by patients with chronic pain treated with narcotics but experiencing breakthrough pain. NDA 20-747 was disapproved 13 November 1997. A statistical review of the original application was conducted by Dr. Yi Tsong. In addition to deficiencies related to chemistry, the action letter cited three concerns related to clinical efficacy and safety. First, questions were raised about blinding in the single pivotal clinical trial. Second, the relationship between adverse events and dose was not well enough characterized to allow an accurate assessment of risk. Third, plans for packaging and marketing to minimize the risk of overdose or accidental exposure were inadequate.

The present submission addresses all these issues. This review focuses on the first two: the question of blinding and its implications with respect to efficacy, and the relationship of adverse events to dose. The questions of risk management are not statistical and will not be taken up here.

Blinding

When NDA 20-747 was initially reviewed, it was noted that some patients reported perfectly constant pain over several assessments, without either the random fluctuations or the subsiding of breakthrough pain that would have been expected. It seemed possible that some patients might have guessed the doses were placebos and filled in a constant level of pain rather than a careful assessment at each timepoint. Investigation by Dr. Mathew Thomas of

the Division of Scientific Investigations showed that a few of these patients did in fact make comments about being able to identify placebos.
Reanalysis by the sponsor of the efficacy data, excluding 14 patients who had constant scores, led to substantially similar conclusions to the original analysis. This submission, however, addresses more broadly the issue of blinding. Case reports and clinical notes were searched for indications of patients' comments on distinguishing the two treatments.

Five patients out of 92 had comments recorded about differences in taste or dissolution. One of the comments was that there was no difference in taste. Of the other four, two said the treatments tasted different, one said the placebo took longer to dissolve, and the fourth said they tasted different *and* the placebo took longer to dissolve.

In addition, 28 patients (including two of the four patients just discussed) made comments about being able to identify active and placebo doses. In many cases the comment specified that the distinction was on the basis of effectiveness; in a few cases side effects were mentioned; but in most cases no basis for the distinction was recorded.

Among the comments of these 28 patients were 57 guesses at the identity of specific dose units. The sponsor cross-tabulated these guesses with the true identity (p. 10-025):

	guessed placebo	guessed OTFC	
received placebo	24	4	28
received OTFC	15	14	29
	39	18	57

The sponsor argues, first, that the number of patients reporting sensory (as opposed to pharmacologic) differences was small; and, second, that the identification was unreliable, as shown by the table. I think both these arguments are weak.

It is true that the number of patients who *reported* sensory differences is too small to matter much. The trouble is that, with one exception (who reported that there was no difference), there is no clear reason to think that other patients did not perceive differences. There is some evidence that the taste and the dissolution of the two formulations were not the same. There is therefore some possibility that patients' responses were influenced by these differences. Excluding patients who reported differences would not solve this problem.

The argument that the identification was unreliable is a curious one, especially supposing, as the sponsor does, that in most cases the identification was on the basis of pharmacologic effect. To say this is to say that the drug was not reliably effective: patients sometimes thought OTFC was placebo precisely because it did not relieve their pain. A drug need not always be reliably effective to be approvable, if it is significantly more effective than the control. By the same token, however, a drug need not be reliably identifiable to raise concerns about blinding.

Notwithstanding the weakness of these arguments, I believe the results of the study are not seriously called into question by concerns about blinding. It is not so easy to produce a matching placebo for a drug that must be held in the mouth and therefore tasted as for a drug that is simply swallowed. It appears that such matching was nevertheless reasonably, if imperfectly, achieved. Many more patients said they found differences in the effects of the formulations than in the taste or dissolution. Their ability to distinguish active from placebo treatments is evidence for rather than against the efficacy of the drug.

A second issue related to blinding concerned the possible use of drug from the open-label titration phase in the double-blind phase. One case report form is quoted as saying, "Patient was in the middle of phase 2 but the hospice nurse (not affiliated with the study) encouraged the family to use phase 1 drug instead so the patient would not receive placebo." This patient and another were found by the sponsor to have done this. However, they appeared also to have used all the blind doses, and the assessments appeared to correspond to the blind doses. A total of 24 patients had some failure to account for drug that was dispensed. Reanalysis without these patients led to substantially similar conclusions regarding efficacy to those in the original report. The sponsor suggests that it is inappropriate to prefer this analysis to the original one because it seems unlikely that the failure in accounting was related to inappropriate dosing. I concur.

Adverse events and dose

The limiting toxicity of narcotics is respiratory depression. The breathing response to carbon dioxide in the blood is inhibited, so that breathing slows or stops, sometimes fatally. Respiratory depression, which is serious and relatively rare, is often accompanied or preceded by somnolence, which is frequent and usually not serious in itself. Accordingly, the incidence of somnolence in studies of narcotics is important.

The integrated summary of safety in the NDA reported the following incidence of somnolence by dose in three studies (200/011, 200/012, 200/013):

200 μg	400 μg	600 μg	800 μg	1200 μg	1600 μg
8/57 (14%)	7/61 (12%)	6/44 (14%)	5/34 (15%)	2/21 (10%)	14/40 (35%)

The dose in this case was defined as the size of the largest unit used by the patient. Patients could take more than one unit for a single episode of breakthrough pain. They could also be given different strengths at different times in the study as a result of titration. The high incidence at 1600 μg caused concern in the original review. Further information was requested associating incidence of somnolence with the actual dose at the time of the adverse event.

A FAX submission (11 September 1997) contained the following information on the incidence of somnolence in the same three studies, labeled as a draft:

dose ≤ 1600 μg	1600 μg < d ≤ 3200 μg	dose > 3200 μg
31/152 (14%)	6/27 (22%)	6/14 (43%)

In this case, the dose was defined as the maximum dose used by the patient for any episode. For example, if a patient ever used two 1600 μg units, but never three, the adverse event would be assigned to the middle category (3200 μg).

These data still left cause for concern about the high incidence at the higher doses, and they still did not link adverse events to a specific dose, but only to the highest dose taken by the patient reporting an adverse event. The present submission contains a reanalysis to address these issues. Adverse events were not unambiguously linked to episodes of breakthrough pain; and since the same patient could take different doses for different episodes, it is therefore impossible to tell with certainty the dose associated with a given adverse event. To respond to the agency's concerns, however, the sponsor attempted to do this to the extent possible. The algorithm is complicated, but in ambiguous cases the adverse event appears to have been assigned to an episode with the highest possible dose. This procedure is conservative in the sense that it would tend to magnify rather than diminish any tendency for adverse events to increase with the dose.

This reanalysis produced the following table (p. 10-203) for somnolence in three studies combined (011, 012 and the titration phase of 013):

200–400 μg	600–1200 μg	1400–1600 μg	1800–3200 μg	>3200 μg
20/745 (2.7%) 18 mild, 2 moderate	28/924 (3.0%) 18 mild, 10 moderate	8/266 (3.0%) 7 mild, 1 moderate	7/158 (4.4%) 6 mild, 1 moderate	1/44 (2.3%) 1 moderate

Note that the unit of analysis is now the episode of breakthrough pain, rather than the patient. So, the fairly small numbers indicate that somnolence was reported in a small fraction of treatment episodes, not in a small fraction of patients. Several pairwise significance tests were carried out, none approaching statistical significance. Such negative significance tests must not be overinterpreted. First of all, as the submission itself points out, the analysis is not technically correct, as the episodes were treated as independent. More importantly, as is usually the case with adverse events, failure to detect a trend is not the same thing as showing there is not a trend. The numbers of events are too small, and therefore subject to too much relative uncertainty, to rule out even a fairly substantial trend. Indeed, the rates do appear to rise substantially from the lowest to the second-highest group, and the highest group is too small to make much impression either way. I do not mean to say there is evidence of a trend. Rather, I mean that there is no real evidence here of the absence of a trend. As to severity, if there is any trend, it is a complex one, with the greatest severity at an intermediate dose.

The submission makes no attempt to reconcile these data with the per-patient analyses submitted earlier. Taken at face value, the analysis leads to the rather strange conclusion that patients prescribed high doses of Actiq have a high incidence of somnolence, but not when they are actually taking the high dose. Other explanations are possible, such as inadequate power to detect the relationship of incidence to actual dose.

Patients for whom high doses were prescribed were, in general, patients with a higher requirement for around-the-clock narcotics in addition. It is not implausible that their high incidence of somnolence was caused by this high dose of other narcotics rather than by Actiq.

Nevertheless, what this study tested was not fixed doses of Actiq but a titration scheme. It is evident that when this scheme indicated high doses of Actiq, the effects included a high incidence of somnolence. This was a concern in the original review of the NDA, and it seems to me that it remains a concern, notwithstanding the new analysis.

Conclusions

This submission adequately addresses concerns about blinding in the pivotal clinical trial. The high incidence of somnolence at high doses remains a concern. Clinical considerations of benefit and risk should determine whether high doses should be approved, and if so how they should be labeled.

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HFD-720/M. Welch, file copy
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HFD-170/division file

NDA Statistical Review and Evaluation (Subgroup Analysis)

NDA#:	20-747
Drug Product:	Actiq™ (Oral Transmucosal Fentanyl Citrate, OTFC), 200, 400, 600, 800, 1200 and 1600 µg tablet
Sponsor:	Anesta Corp.
Indications:	For management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy
Received Date:	October 10, 1997
Documents Reviewed:	Subgroup Analysis
CSO:	Ken Nolan
Complete Date:	
Medical Reviewer:	Roberta Kahn, MD
Primary Reviewer:	Yi Tsong, PhD
Secondary Reviewer:	Thomas Permutt, PhD, Nancy Smith, PhD

Introduction

In response to FDA's October 2, 1997 request, the sponsor performed subgroup analysis for older (age≥60 years) patients and for female patients of AC200/013 clinical trial study. The subgroup analysis was carried out on the dose level, efficacy and safety.

Age group analysis

In the age group analysis, titration success rate, maximum dose level during titration phase, OTFC dose level, efficacy and safety during the double blind phase of the older patients were assessed and compared with the patients under 60.

i). Background - Of the 130 patients enrolled into the study, 43 (33%) patients were 60 years or older. At baseline, 32 of these patients (74%) used oral opioid ATC, 29 (67%) patients used oral opioid as rescue medication, 10 (23%) patients used OTFC around the clock (ATC) and 7 (16%) patients used OTFC as rescue medication at baseline and in titration phase. The dose levels of the medication in morphine equivalence were 160 mg/day of oral opioid ATC, 17 mg/episode of oral opioid rescue, 78 µg/hr of OTFC ATC and 6 mg/episode of OTFC rescue. There is no difference proportion difference between the two groups.

ii). Titration success rate - Thirty-two of older patients (74%) completed the titration phase and entered the double blind phase. Of those entered the double blind phase, 23 (72%) completed all 10 episodes. In other words, 53% of those enrolled into the study were titrated successfully and completed all 10 episodes in double blind phase. The proportion was not significantly different to those of 59 years old or younger patients.

iii). Dose level analysis - Sponsor's analysis on dose level for the two age groups is summarized in Table 1. There was no significant difference in dose level between the younger and older patient groups. During the titration phase, the mean of maximum total dose per episode of OTFC in older group was 929 µg. It was not statistically different (p=0.15) from the mean maximum dose of 1221 µg/episode in younger patients. In the double blind phase, the mean OTFC dose level used in the older group was 650 µg/episode which is significantly lower than the younger group (mean=863 µg/episode, p=0.04).

Table 1 Baseline Characteristics and Dose Level by Age

	≥ 60 yrs old	≤ 59 yrs old	p-value
Baseline			
Received drug and entered titration phase N (%)	43	87	
Gender Female Male	21(49) 22(51)	54(62) 23(38)	
Medication Level at baseline			
Patients taking oral opioid ATC Number of patients Mean level (SD)	 32 160(119)	 65 199(165)	 0.24
Patients taking oral opioid rescue Number of patients Mean level (SD)	 29 17(18)	 54 21(19)	 0.41
Patients taking OTFC ATC Number of patients Mean level (SD)	 10 78(32)	 21 107(61)	 0.16
Patients taking OTFC rescue Number of patients Mean level (SD)	 7 6(3)	 14 15(15)	 0.15
Titration Phase			
Completed titration phase and entered double blind phase	32(74)	60(70)	
Gender Female Male	16(50) 16(50)	35(58) 25(42)	
Maximum total dose per episode in titration phase			
Median	800µg	800µg	
75 percentile	1200µg	1600µg	
90 percentile	1600µg	2400µg	
Mean	929µg	1221µg	0.15

Double Blind Phase			
Completed 10 episodes in double blind phase	23(53)	49(56)	
OTFC dosage during double blind phase			
Median	600μg	800μg	
Mean	650μg	863μg	0.04

iv). Efficacy Analysis - Sponsor's analysis of efficacy stratified by age group is summarized in Table 2. The older group had consistently lower mean score than the younger group at all time points at and after treatment in both OTFC and placebo treatment. The differences were statistically significant with p-values ranging form 0.046 to 0.01 in ANOVA. The treatment efficacy was also shown significant consistently in both groups at all time points except at time=0 minute. Older patients had larger reduction by OTFC treatment than the younger patients consistently. However, the differences were not significant. The similar results were also shown in pain relief score. OTFC treatment had higher pain relief score than placebo at all time points in both age groups. In the three-way ANOVA with age group, treatment and treatment-by-age group interaction as factors, p-value of age group factor and age-by-treatment were not significant. Hence we may conclude that the treatment was as effective in older patients as in the younger ones in both endpoints.

Table 2 Efficacy by Age group

Difference	0 min	15 min	30 min	45 min	60 min
Pain Intensity Score (Placebo-OTFC)					
Age≥60 yrs(mean/p-value)	0.28 /0.049	0.88 /0.0009	1.14 /0.0004	1.12 /0.008	1.28 /0.002
Age≤59 yrs(mean/p-value)	0.07 /0.40	0.67 /0.0004	1.00 /<0.0001	1.11 /<0.0001	1.17 /<0.0001
ANOVA p-value age age*treatment	 0.04 0.24	 0.02 0.51	 0.01 0.72	 0.02 0.98	 0.046 0.83
Pain Relief Score (OTFC-Placebo)					
Age≥60 yrs(mean/p-value)		0.63 /0.0002	0.75 /0.0001	0.75 /0.001	0.97 /<0.0001
Age≤59 yrs(mean/p-value)		0.42 /0.0004	0.66 /<0.0001	0.68 /<0.0001	0.73 /<0.0001
ANOVA p-value age age*treatment		 0.64 0.30	 0.06 0.71	 0.08 0.80	 0.07 0.40

v). **Safety analysis** - The younger age group had significantly more cases of somnolence (2% vs. 17% with odds ratio=6.06). Otherwise there was no outstanding difference between the groups in the selected most frequent adverse events (including asthenia, pain, diarrhea, nausea, vomiting and dizziness).

vi). Conclusion on age group analysis

As shown in sponsor's analysis, about same proportion of enrolled patients in patients 60 years or older and in younger patients were titrated successfully and then completed all 10 episodes of treatment in double blind phase. During the titration phase, older patients had lower maximum total OTFC dose per episode than the younger patients. But the difference is not significant (929 μg versus 1221 μg, p=0.15). However, during the double blind phase, the mean OTFC dose levels were 650 μg for older patients and 863 μg for younger patients. The difference was statistically significant (p=0.04, t-test). OTFC treatment was shown to be effective in both groups in pain intensity score and in pain relief score during the double blind phase. In older patients, the differences between placebo and OTFC treatments in pain intensity score were significant at 0 minute (Difference=0.28, p value =0.049) and increased to 60 minutes (difference=1.28, p value =0.02) after administration. In younger patients, the differences were significant at 15 minutes (difference=0.67, p value=0.0004) and increased to 60 minutes (difference=1.17, p value <0.0001) after the administration. Similarly, in older patients, differences between OTFC and placebo treatments in pain relief were significant at 15 minutes (difference=0.63, p value =0.0002) and increased to 60 minutes (difference= 0.97, p value <0.0001) after administration. In younger patients, the differences were significant at 15 minutes (difference=0.42, p value =0.0004) and increased to 60 minutes (difference= 0.73, p value <0.0001) after the administration. Over all time points, there was no significant difference in OTFC efficacy between the old and young groups. There was no significant difference in adverse reactions between the two groups except that there were significantly more cases of somnolence in younger patients.

<u>Gender group analysis</u>

i). Background - Of the 130 patients enrolled into the study, 75 (58%) patients were female. . At baseline, 57 (76%) female patients used oral opioid around the clock (ATC), 51 (68%) patients used oral opioid as rescue medication, 17 (23%) patients used OTFC ATC and 14 (19%) patients used OTFC as rescue medication at baseline and in titration phase. The dose levels of the medication in morphine equivalence were 212 mg/day of oral opioid ATC (149 in males, p=0.04), 20 mg/episode of oral opioid rescue (20 in males, p=0.95), 87 μg/hr of OTFC ATC (111 in males, p=0.23) and 7 mg/episode of OTFC rescue (18 in males, p=0.052).

ii). Titration success rate - Fifty-two (69%) of female patients completed the titration phase and entered the double blind phase. Of those who entered the double blind phase, 39 (76%) completed all 10 episodes. In other words, 52% of those enrolled into the study were titrated successfully and completed all 10 episodes in double blind phase. This proportion was not significantly different to male patients (60%).

iii). Dose level analysis - Sponsor's analysis on dose level for the two gender groups is summarized in Table 3. There was no significant difference in dose level between the two gender groups. During the titration phase, the mean of maximum total dose per episode of OTFC in female group was 1065 µg. It was not statistically different (p=0.46) from the mean maximum dose of 1207 µg/episode in male group. In the double blind phase, the mean OTFC dose level used in the female group was 737 µg/episode which was not significantly lower than the male group (mean=854 µg/episode, p=0.24).

Table 3 Baseline Characteristics and Dose Levels by Gender

	Female	Male	p-value
Received drug and entered titration phase N (%)	75	55	
Medication Level at baseline			
Patients taking oral opioid ATC Number of patients Mean level (mg/day)(SD)	 57 212(166)	 40 149(123)	 0.24
Patients taking oral opioid rescue Number of patients Mean level (mg/episode)(SD)	 51 20(17)	 32 20(22)	 0.41
Patients taking OTFC ATC Number of patients Mean level (µg/hr)(SD)	 17 87(52)	 14 111(56)	 0.16
Patients taking OTFC rescue Number of patients Mean level (morphine eq mg/episode)(SD)	 12 7(3.9)	 9 18(18)	 0.15
Titration Phase			
Completed titration phase and entered double blind phase	52(69)	41(75)	
Maximum total dose per episode in titration phase			
Median	800µg	800µg	
75 percentile	1600µg	1600µg	
90 percentile	2400µg	2400µg	
Mean	1065µg	1207µg	0.46
Double Blind Phase			
Completed 10 episodes in double blind phase	39(52)	33(60)	
OTFC dosage during double blind phase			
Median	600µg	800µg	
Mean	737µg	854µg	0.24

iv). Efficacy analysis - Sponsor's analysis of efficacy stratified by gender group is summarized in Table 4. OTFC treatment was effective in comparison with placebo in both gender group at 15 minutes and later time points after administration. There was no consistent difference between the gender groups in pain intensity score or pain relief score. This was verified with the nonsignificant p value >0.05 at all time points in both pain intensity and pain relief scores for gender-by-treatment interaction in the three-way ANOVA.

Table 4 Efficacy by Gender

Difference	0 min	15 min	30 min	45 min	60 min
Pain Intensity Score (Placebo-OTFC)					
Female(mean/p-value)	0.20 /0.007	0.78 /0.0002	0.95 /0.0002	0.94 /0.002	1.03 /0.002
Male(mean/p-value)	0.07 /0.54	0.69 /0.0003	1.16 /<0.0001	1.33 /<0.0001	1.42 /<0.0001
ANOVA p-value Gender Gender*treatment	 0.80 0.44	 0.94 0.74	 0.76 0.56	 0.99 0.36	 0.82 0.41
Pain Relief Score (OTFC-Placebo)					
Female(mean/p-value)		0.55 /<0.0001	0.64 /<0.0001	0.65 /0.0004	0.76 /<0.0001
Male(mean/p-value)		0.43 /0.003	0.75 /<0.0001	0.77 /0.0002	0.88 /<0.0001
ANOVA p-value Gender Gender*treatment		 0.40 0.54	 0.74 0.66	 0.79 0.65	 0.95 0.66

v). Safety analysis - There was no significant difference between the gender groups in cases of selected most frequent adverse events (including asthenia, fever, pain, diarrhea, nausea, vomiting, dyspnea).

vi). Conclusion on gender group analysis

There were slightly higher percentage of male patients completed titration phase and completed all ten episodes of double blind phase than the female patients. Female patients had lower maximum OTFC dose per episode in the titration phase than male patients (mean 1065μg in female and 1207μg in male, p=.46). But the difference was not significant. In double blind phase, female patients used an average of 737 μg of OTFC/episode and male patients had 854 μg/episode. The difference was also not significant. OTFC treatment was effective in both male and female patients as shown in double blind phase. In female patients, the differences between placebo and OTFC in pain intensity score were significant at all time points and the difference increased from 0 minute (placebo-OTFC=0.20, p=0.007) and increased to 60 minutes (difference=1.03, p=0.002) after administration. In male patients, difference increased also from

0 minute (difference=0.07, p=54) to 60 minutes (difference=1.12, p value<0.0001) after administration. The differences were significant at all time points after 15 minutes (differnce=0.69, p=0.0003). Similarly, OTFC-placebo difference in pain relief increased from 15 minute (0.55, p<0.0001) to 60 minutes (0.76, p<0.0001) after administration in female patients. The same patten aso held in male patients. The differences were statistically significant at all time points. There was no statistically significant difference in OTFC efficacy between the gender groups. There were no significant difference in frequency of adverse events between the gender groups.

Conclusion

The reviewer agrees with the analysis performed by sponsor in assessing dose level, efficacy and safety difference between male and female or between patients older than 60 yrs and younger. From the analysis, the results can be summarized as follows

1) Patients of 60 years or older used lower level of dose for breakthrough pain than the younger patients. Eighty percent or more patients 60 years of age or older had 800 µg/episode or less with the mean dose being 650 µg/episode in double blind phase. The mean dose level was significantly lower than the younger age group. With the lower dose level, the OTFC treatment was effective in pain intensity and pain relief in older patients. It was also shown in the double blind phase that older patients had significantly lower pain intensity under either OTFC or placebo treatment than younger patients. There was no significant difference in safety between the two age group except significantly fewer somnolence cases in older patients;

2) For patients using oral opioid ATC, female patients had higher dose level than the male users. But there was no difference in per episode maximum OTFC dose level in titration phase or mean OTFC dose level between the two genders. OTFC treatment was effective in both male and female patients with no difference in cases of adverse events.

/S/

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NDA Statistical Review and Evaluation

NDA#:	20-747
Drug Product:	Actiq™ (Oral Transmucosal Fentanyl Citrate, OTFC), 200, 400, 600, 800, 1200 and 1600 μg tablet
Sponsor:	Anesta Corp.
Indications:	For management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy
Received Date:	Nov. 13, 1996
Documents Reviewed:	Vol. 1.2, 1.25-1.32, Anesta Study AC400/001, AC 200/006, AC200/011, AC200/012, AC200/013, AC200/0P10, AC200/010
CSO:	Ken Nolan
Complete Date:	July 15, 1997
Medical Reviewer:	Roberta Kahn, MD
Primary Reviewer:	Yi Tsong, PhD
Secondary Reviewer:	Thomas Permutt, PhD, Nancy Smith, PhD

Table of Content

I. Introduction

Actiq™ (Oral Transmucosal Fentanyl Citrate, OTFC), 200, 400, 600, 800, 1200 and 1600 μg tablet is under development by the sponsor for the management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy. The sponsor has submitted seven trials in support of the claims. Trials AC200/011 and AC200/012 are titration trials for management of chronic pain. AC200/013 was submitted in support of the claim for the management of chronic pain. AC200/010 was submitted in support of the dose equivalence claim. AC200/0P10 is a pilot trial for AC200/010. The two trials AC400/001 and AC200/006 were originally designed to study OTFC efficacy and safety for the management of acute pain in postoperative patients.

II. Clinical Trials in Patients with Acute Pain

II.1. AC400/001 - Compassionate use of oral transmucosal fentanyl citrate (OTFC) in patients with postoperative pain.

II.1.1 Study Design

AC400/001 is a randomized, double-blind, placebo-controlled, single center trial. PCA morphine analgesia was initiated in the post analgesia care unit (PACU) just prior to transferring the patient to the patient care unit. On the morning following surgery, the previous twelve hours of PCA data were recorded to establish a baseline, and patients were then given study drug every four hours for twelve hours while continuing PCA treatment. Data collection and PCA treatment continued for twelve additional hours. Following each OTFC administration, assessments of vital signs, oxygen saturation and PCA morphine administration were made by investigators. The patients in the active treatment group were treated with 7-10 mcg/kg per administration.

II.1.2 Inclusion/Exclusion Criteria-

The inclusion criteria were

1) Patient with total joint replacement
2) Age between 18 and 80 years
3) Weight 40-100 kg
4) ASA I, II, III
5) Signed and dated written consent

Patients were excluded if they had a history of drug abuse, chronic pain medications, known or suspected allergies to medication used in the study, or were not scheduled to undergo total joint replacement.

II.1.3 Study Sample Size

The study was planned to enroll forty patients into the study with twenty patients randomly assigned into each treatment group. No sample size estimation based on target treatment effect

size was given.

The actual number of patients evaluable for the efficacy analysis is 13 in placebo group and 15 in OTFC group. The numbers of patients enrolled, entered into the study and evaluated are given in Table II.1.1.

Table II.1.1 Numbers of patients enrolled, entered and evaluable for efficacy study

	Placebo	OTFC	None
To be Enrolled	**20**	**20**	**-**
Entered Study	**19**	**19**	**-**
Nonevaluable	**6**	**4**	**-**
Protocol Violation	**1**	**1**	**-**
Patient Withdrawal	**3**	**2**	**-**
Failure to PCA Delivery System	**1**	**1**	**-**
Incomplete Data	**1**	**0**	**-**
Did not receive Study Drug	**-**	**-**	**1**
Evaluable	**13**	**15**	**-**

II.1.4 Sponsor's Analysis

Baseline Data -

The baseline information collected includes

Demographics -	age, height in inches, weight in kg, sex, race, the presence of allergies (type and reaction), and use of chronic medications (name, dose route of administration, date last taken).
Medical History-	abnormality of neck and head, cardiovascular, respiratory, gastrointestinal, genitourinary, skin, and central nervous body systems
Physical Examination -	existing abnormalities for head, lung, heart, abdomen, extremities, skin, and neurologic body systems
Procedure-	all surgical procedures taken

Patients in placebo group and OTFC group were compatible regarding to the information collected at baseline. There is no statistical difference between placebo and treatment groups in age, weight, height, sex, ASA class, surgical procedure (Table 1, vol. 1.27 pp10-746 of NDA submission), allergy (Table 2, vol. 1.27 pp10-747 of NDA submission), chronic medication (Table 3, vol.1.27 pp 10-748 of NDA submission), medical history (Table 4, vol. 1.27 pp10-749 of NDA submission), physical examination (Table 5, vol.1.27 pp10-750 of NDA submission).

Efficacy Endpoints and Testing Hypotheses -

There were three efficacy endpoints collected in this trial. The measurements were grouped into Baseline (1-12 hour), Admin (13-24 hour), Post-Admin (25-36 hour). The measurements during Admin period were also grouped into Admin #1 (13-16 hour), Admin #2 (17-20 hour) and Admin #3 (21-24 hour). The analyses were done by both comparing the OTFC treatment with placebo of response at each period and with the responses across all periods as repeated measures

by using statistical models with period as one factor .

The efficacy endpoints are
1) Attempts: the PCA pump had a lockout time of 10 minutes, so the pump did not respond to all requests for additional analgesia. The number of attempts was the number of times the button was pushed. The distribution of pump attempts is skewed and the analyses were carried out by non-parametric procedures.
2) Injection: The number of injections received by each patient per hour
3) Morphine Dose: The dose of morphine (in mg) injected per hour

Analysis
Mean values of the efficacy endpoint were compared using the analysis of repeated measurements across three administrations. The methods of analysis are given more specifically below. To assure that the difference was not due to potential difference of the patients, comparison of mean values at baseline and post-administration were also made to show that the differences were not statistically significant.

1) Attempts - Number of attempts in each period was ranked and the ranks of a patient at all the periods were taken as repeated measures of the patients. The mean rank of OTFC and placebo group was then compared using SAS procedure CATMOD. With CATMOD, comparison was made by using an ANOVA model with categorical outcomes and with group, period and group-by-period interaction as factors. It was shown that there was significant group-by-period interaction ($p=0.032$) (See Table II.1.2) when the three periods used in the analysis were baseline period, administration period and post administrations period. It was further shown that through analysis by period, there was no significant difference between treatment and placebo groups at both baseline ($p=0.730$ using Mann-Whitney rank sum test, $p=0.119$ using chi-square approximation test) and post-administration ($p=0.518$ using Mann-Whitney rank sum test and $p=0.418$ using chi-square approximate test). The mean number of attempts was significantly higher in placebo group ($p=0.009$) when mean responses at the three administrations were compared using CATMOD procedure with the administrations as the period factor.

2) Injections per hour - Distribution of number of injections was assumed to be normal and comparison of mean number of injections at baseline, administration and post-administration period were compared using ANOVA for repeated measurements with group, period and group-by-period interaction as three factors. It was shown that there was significant group-by-period interaction ($p=0.010$). The mean values of injections per hour of treatment and placebo were compared at baseline and postadministration period separately using t-test. There is no significant difference in either of the two periods. These results indicates that OTFC provided pain relief effect during the administration period. It shows also that OTFC patients received significantly fewer injections than placebo patients ($p=0.019$ for repeated measurement analysis)

3) Morphine dose - Morphine dose per injection was adjusted for the body weight. The dose ranged from 0.6 mg to 1.6 mg per injection in the study. OTFC patients had less average dose

than the placebo group (p=0.035 for repeated measurement).

Table II.1.2 Analysis of efficacy endpoints

Treatment group	Time interval					
	Baseline (1-12 hr)	Admin (13-24 hr)	Post Admin (25-36 hr)	Admin #1 (13-16 hr)	Admin #2 (17-20 hr)	Admin #3 (21-24 hr)
Mean Attempts/Hr/Patient						
Placebo n=13	2.90	2.12	1.50	2.28	1.75	2.33
OTFC n=15	2.96	0.81	1.22	1.00	0.82	0.60
P-value of Mann-Whitney U-test	0.730[1]	-	0.518	-	-	-
P-value of Chi-Square Approx. Test[1]	0.119	-	0.418	-	-	-
P-value of ANOVA Repeated Measurement analysis						
Group	0.237			0.009		
Period	0.981			0.999		
Group*Period	0.032			0.841		
Mean Injections/hr/patient						
Placebo n=13	1.250	1.090	0.744	1.212	1.115	0.942
OTFC n=15	1.339	0.489	0.683	0.550	0.483	0.433
P-value of t test	0.668	-	0.418	-	-	-
P-value of ANOVA Repeated Measurement analysis						
Group	0.247			0.014		
Period	0.000			0.173		
Group*Period	0.010			0.730		
Mean Total Dose in mg/patient						
Placebo n=13	1.231	1.220	0.806	1.288	1.165	1.206
OTFC n=15	1.508	0.532	0.744	0.600	0.513	0.482
P-value of t test	0.246	-	0.781	-	-	-
P-value of ANOVA Repeated Measurement analysis						
Group	0.433			0.035		
Period	0.000			0.723		
Group*Period	0.005			0.970		

1: Testing for H_0: $p_{1k} = p_{2k}$, k=1... K category of number of attempts

Analysis of Safety Measurements

Three safety measures in the protocol were identified as follow:

1) Vital signs: Heart rate, systolic blood pressure, diastolic blood pressure and respiratory rate were recorded just prior to receiving each OTFC dosage unit and at 15 minute intervals for one hour.

2) Oxygen Saturation: Oxygen saturation was continuously monitored using a pulse oximeter with the noninvasive probe attached to the patient's finger. Oxygen saturation was recorded at the same times as the vital signs. Oxygen saturation less than 90% for 30 seconds was defined to be clinically significant.

3) Adverse Effects: Type of adverse effect was recorded along with onset time, severity and relationship to the study drug. The severity of the effect was evaluated using the following scales:

Degree of severity	Score
Mild, limited, no treatment, full recovery ...	1
Moderate, required some treatment, full recovery ...	2
Severe, prolonged, required medical intervention and/or hospital admission ...	3

Relation to OTFC	
Unrelated ...	1
Possibly related ...	2
Probably related ...	3
Definitely related ...	4

The mean values of heart rate (in beats/min), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg) respiration rate (in breaths/min) and oxygen saturation (in percent) by each of the 15 minutes intervals after each of the three OTFC dosage by treatment group are given in Tables 18-22. It is shown that the average heart rates and diastolic blood pressure of OTFC patients were higher than placebo and average breaths/minute is lower in OTFC patients during all three OTFC administrations. However, there was no statistical difference in the mean values of the safety measurement between the OTFC and placebo group when they were analyzed using ANOVA model with responses as repeated measurement.

There was no significant difference between OTFC and placebo patients in changes from baseline in vital signs and oxygen saturation rate as shown in Figures 4 to 8 (page 10-741 to 10-745 of NDA submission) and shown in repeated measurement analyses.

Lowest vital signs and oxygen saturation results and comparative analyses were given in Table 28 and 29 of NDA submission. They are summarized in the following table.

Table II.1.3 Analysis of Lowest Vital Signs and Oxygen Saturation

Treatment group	Vital Signs and Oxygen Saturation				
	Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Respiratory Rate (bpm)	Saturation Prop of Oxygen (%)
Placebo n=13					
Minimum	49	95	48	8	70
Maximum	98	160	78	18	98
Mean	73	115	63	13	88
Standard Dev	13	16	8	4	7
OTFC n=15					
Minimum	63	98	54	10	74
Maximum	96	132	80	18	94
Mean	77	112	66	12	89
Standard Dev	10	12	8	3	5
Comparison of Mean Difference Between OTFC and Placebo (test p-value)					
Bartlett Test	0.5	0.340	0.865	0.193	0.186
T-test (H_o:Diff=0)	0.4	0.681	0.249	0.399	0.904
Time to Lowest Vital Signs and Oxygen saturation (Minutes from Start of First Administration)					
Placebo					
Maximum	525	510	510	495	525
Mean	160.39	174.23	291.92	174.23	310.39
Standard Dev	187.99	60	285	60	170
Median	60	60	285	60	60
OTFC					
Minimum	0	60	45	15	15
Maximum	480	540	540	540	540
Mean	163.00	369.00	294.00	195.00	255.00
Standard Dev	155.56	155.35	185.78	179.82	200.13
Median	45	300	285	240	270
Comparison of Mean Difference Between OTFC and Placebo (test p-value)					
Mann-Whitney U Test	0.834	0.005	0.963	0.660	0.798

Analysis of Adverse effects

The adverse effects reported in the trial included nausea, vomiting, itching, decreased oxygen saturation, sweating, warmth, tachycardia, blurred vision, rhinitis, drowsiness, disoriented. The effects were reported from both OTFC and placebo groups. Itching was reported from OTFC

patients only (3 patients and 7 occurances in OTFC versus 0 in placebo pts), but the difference is not statistically significant. The total number of occurrences of adverse effects are 52 in OTFC patients versus 18 in placebo patients. Since the distributions of the number of occurrences is skewed (with mode at 0 occurrence for OTFC and 1 occurrence for placebo), the comparison of the difference in number of occurrences between the two groups was carried out using nonparametric tests. The following are the p-values of the comparisons using different nonparametric tests. The sponsor reported the non-significant p-value using the commonly used Mann-Whitney rank sum test.

Table II.1.4 Analysis of Adverse Effects

Total Number of Adverse Effect Occurances by Patients			Significant Test	p-value
Number of Occurances	Placebo (N=13)	OTFC (N=15)		
0	3	5	Mann Whitney 2-sample test (Rank sum test)	0.116
1	6	0	Kruskal-Wallis test (Chi-square approximation)	0.111
2	1	1	Test for equal median (Chi-square approximation)	0.063
3	1	1		
4	1	1		
5	0	3		
6	0	2		
7	0	1		
9	0	1		
Total Occurances	18	52		

II.1.5 Reviewer's Evaluation

The sample size of the trial was not calculated by statistical estimation based on a target of a specific treatment effect size, and the primary efficacy endpoint, the number of attempts for additional analgesia, was determined after the trial was completed rather than pre-specified in the protocol. However, the study result showed that patients treated with 7-10 mcg/Kg OTFC had better responses than placebo patients in all three pre-specified efficacy endpoints through analysis of repeated measurement at three administrations. Patients treated with OTFC had lower mean value than placebo in number of attempts (p=0.009), injections (p=0.014) and in total dosage of morphine (p=0.035) (See Table I.1.2).

The safety of the treatment was assessed in two sets of measurements. OTFC is comparable with placebo in changes from baseline on vital signs (heart rate, systolic and diastolic blood pressure,

respiration rate, lowest vital sign and oxygen saturation) (See Table I.1.3), the lowest measurement of the vital sign during the administrations (See Table I.1.4). There were no significant difference in time from the start of the first administration to the lowest measurement in all measurements except for lowest systolic blood pressure (See Table I.1.4). This study showed that on average it took placebo patients significantly less time to reach lowest systolic blood pressure than patients treatment with OTFC. Although there were more adverse effects in OTFC patients than in placebo patients (52 in OTFC versus 18 in placebo), the difference is not statistically significant.

II.2 AC200/006 - Morphine sparing effect of Oral Transmucosal Fentanyl Citrate (OTFC) in patients experiencing acute postoperative pain.

II.2.1 Study Design

The trial consisting of two centers
is a randomized, double-blind, three-arm (placebo, 400 μg and 800 μg of OTFC), placebo-controlled trial in patients using intravenous morphine sulfate via PCA. American Society of Anesthesiology (ASA) physical status I-III patients undergoing hip or knee arthroplasty were enrolled in the study. After emergence from anesthesia in the post anesthetic care unit and regaining consciousness and after the first request of analgesia, patients received 400 μg, 800 μg of OTFC or placebo by random assignment. Intravenous PCA morphine was initiated and patients were encouraged to use the PCA to supplement the study drug as necessary in order to maintain adequate analgesia. The study drug was administered every three hours for twelve hours.

Efficacy and safety assessment of the study include PCA morphine attempts, infusions, total dose of morphine used, patient evaluated level of pain intensity, patient pain assessment prior to the second, third and fourth administrations, sedation, vital signs (including blood pressure, heart rate and respiratory rate), usage of naloxone, oxygen, cardiac stimulants. The following is the time table of the assessments.

Table II.2.1 Table Time Table of Efficacy Assessment

Scheduled Time	Study Drug Administration	PCA Data	Pain Intensity (VSA)	Global Assessment of Pain	Vital Signs	Sedation
Baseline (0 min)	x	x	x		x	x
15 min			x		x	
30 min			x		x	
45 min			x		x	
60 min		x	x		x	x
120 min		x	x		x	x
180 min	x	x	x	x	x	x
195 min			x		x	
210 min			x		x	
225 min			x		x	
240 min		x	x		x	x
300 min		x	x		x	x
360 min	x	x	x	x	x	x
375 min			x		x	
390 min			x		x	
405 min			x		x	
420 min		x	x		x	x
480 min		x	x		x	x
540 min	x	x	x	x	x	x
555 min			x		x	
570 min			x		x	
585 min			x		x	
600 min		x	x		x	x
660 min		x	x		x	x
720 min		x	x		x	x

II.2.2 Inclusion/Exclusion Criteria

The inclusion criteria were

1) Patients scheduled to undergo joint arthroplasty of hip or knee
2) Age between 18 and 79 years
3) Male or female
4) ASA class I, II, III

5) Signed and dated written consent prior to surgery
6) Patient weight between 40 and 100 kg
7) Capable of understanding PCA procedure

Patients were excluded from the trial with any of the following conditions,
1) History of significant drug or alcohol abuse in previous year
2) Pregnancy
3) Received an experimental drug in the previous four weeks
4) Incapable of operating of PSA device
5) Usage of hydromorphone, morphine, or meperidine for five consecutive days in the week proceeding surgery
6) Known or suspected allergies to medication used in the study
7) Received intraoperative morphine.

II.2.3 Study Sample Size

One hundred fourteen patients received at least one administration of the study drug. No sample size estimation was given in NDA. The numbers of patients receiving the administration of the study drug are given in the following table.

Table II.2.2 Numbers of Patients Received Treatment

Administration	Placebo	400 µg OTFC	800 µg OTFC
Administration #1	33	34	34
Administration #2	31	30	31
Administration #3	26	29	22
Administration #4	24	28	21
At least one administration	37	40	37

II.2.4. Sponsor's Analysis

Baseline Data -

The baseline information collected in the trial includes

Demographics - age, height in inches, weight in kg, sex, race
Procedure- surgical procedures taken

Sponsor found no statistical difference between placebo and treatment groups in age, weight, height, sex, ASA class, surgical procedure (Table 5, vol. 1.27 pp10-598 of NDA submission). There is statistically significant difference between the treatment groups in the surgical procedures taken. A significantly larger proportion of patients given 800 µg OTFC than other study drugs in had free vascularized fibular bone graft, while a significantly larger proportion of patients in 400 µg OTFC group than the other groups had knee arthroplasty. The difference in surgical procedures is not expected to affect the study results.

Table II.2.3. Proportions of Baseline Information

	0	400	800	0	400	800	Total 0	400	800	p-value Trt	Cntr	Trt*Cntr
No of Pts	16	18	16	21	22	21	37	40	37	-	-	-
Sex[a] Female/Male	11/5	10/8	9/7	10/11	10/12	4/17	21/16	20/20	13/24	0.16	na	na
ASA[b] I/II/III	3/11/2	3/13/2	5/9/2	1/17/3	5/14/3	4/16/1	4/28/5	5/14/3	4/16/1	0.61	na	na
Age[c] Mean(SD)	52(16)	54(14)	58(16)	54(14)	47(16)	44(14)	53(15)	50(15)	50(16)	0.78	0.03	0.09
Height[c] Mean(SD)	167(7)	168(10)	170(11)	169(10)	170(10)	174(11)	168(9)	169(10)	172(11)	0.25	0.20	0.86
Weight[c] Mean (SD)	75(12)	74(16)	76(11)	78(15)	83(14)	84(11)	76(14)	79(15)	81(12)	0.48	0.01	0.53
Race[d] White	16	15	15	20	20	17	36	35	32	0.22	na	na
Black	0	0	0	1	2	4	1	2	4			
Hispanic	0	2	1	0	0	0	0	2	1			
Am. Ind	0	1	0	0	0	0	0	1	0			

a: Chi-square test with 2-by-2-by-3 table; b: Chi-square test with 2-by-3-by-3 table; c:Two way ANOVA, d: Chi-square test for white vs. non-white with 2-by-2-by-3 table.

Table II.2.4. Analysis of Proportion of Medical Procedures (Continued)

	0	400	800	0	400	800	Total 0	400	800	p-value[@] Trt	Heterogeneity
Number of Patients	16	18	16	21	22	21	37	40	37	-	-
Free Vascularised Fibular Bone Graft (%)	0(0)	0(0)	0(0)	2(10)	6(27)	12(57)	2	6	12	<0.001	
Hip Arthropasty (%)	14(88)	13(72)	14(88)	17(81)	9(41)	7(33)	31	22	21		
Knee Arthroplasty (%)	1(6)	4(22)	2(12)	1(5)	7(32)	2(10)	2	11	4		
Other (%)	1(6)	1(6)	0(0)	1(5)	0(0)	0(0)	2	1	0		

@: Mantel Haenszel Test for Stratified Tables

Among the eighty-eight patients who had consumption time recorded for all four administrations, there was a statistically significant difference between the centers and among the four administrations, but there was no significant difference among the study groups and no significant interaction between study group and center or administration. Hence, there is no impact of consumption time on the interpretation of the study results. (Table 7, vol. 1-27 pp10-599 of NDA)

Analysis of Efficacy Endpoints -

Some patients had protocol violations or withdrew from the study before completing all four administrations of study drug. The patient's evaluablity was determined after study completion and before study blind was broken. As a result, patients were considered evaluable for efficacy up to the administration period in which the protocol violation or withdrawal occurred.

There were 55 protocol violations in 35 patients. The most common violations were initiation of

PCA before consumption of study drug was complete. For the first administration, there were 101 evaluable patients (33 placebo, 34 in 400 μg, 34 in 800 μg OTFC group). By the fourth administration, the number of evaluable patients was reduced to 73 (23 received placebo, 28 received 400 μg, 21 received 800 μg OTFC). The number of and reasons for withdrawals are given in the Safety Analyses Section.

Endpoints -
The efficacy endpoints analyzed are
1.Morphine Use - The morphine use of the patients in each of the four administration periods (hours 0-3, hours 4-6, hours 7-9 and hours 10-12). This endpoint is taken as the primary efficacy endpoint.

2. Morphine Equivalency - The morphine sparing effect of OTFC which was calculated by taking the difference in morphine use between OTFC dose and placebo groups and dividing by the amount of morphine use of OTFC group, were evaluated. Because the study was not design to study morphine equivalency, this was taken as secondary endpoint.

3. Visual Analog Score (VAS)

4. Global Pain Evaluation - Patients rated their pain using a 6-point scale (1=none through 6=excruciating) before study drug administration in the second, third and fourth administration periods.

5. Sedation

Analysis of primary endpoints:
Morphine Usage - When an analysis was done for each administration period (using patients evaluable in the period only), patients who received the 800 μg dose of OTFC required less morphine during the first two administration periods than either the placebo or the 400 μg OTFC dose groups (all p values ≤ 0.02, Dunn's multiple comparison following Kruskal-Wallis test). There were no statistically significant difference between the 400 μg OTFC dose and placebo groups.

Table II.2.5 Time Interval Analysis of Variance of Morphine Usage

	Hours 0-3	Hours 4-6	Hours 7-9	Hours 10-12
Placebo				
n	33	31	26	24
Mean Morphine (mg)	12.3	7.7	5.3	4.0
SD	7.8	6.3	5.8	5.2
400 µg OTFC				
n	34	30	29	28
Mean Morphine (mg)	13.0	7.0	5.7	5.8
SD	10.4	5.8	4.7	5.2
800µg OTFC				
n	34	31	22	21
Mean Morphine (mg)	7.6	4.3	4.3	3.3
SD	7.8	5.6	5.5	3.5
P-value				
Among Treatment*	0.011	0.008	0.24	0.17
400µg vs. placebo**	0.94	0.58	0.67	0.60
800µg vs. placebo	0.011	0.004	0.23	0.20
800µg vs. 400µg	0.009	0.02	0.10	0.07

*: Kruskal-Wallis test; ** Dunn's Multiple Comparison following Kruskal-Wallis test.

In the repeated measurement analysis (included all administration periods), only patients evaluable at all administration periods (24 in placebo, 28 in 400 µg and 21 in 800 µg dose groups) were included. Patients received the 800 µg OTFC used less morphine during the four administration period than patients who received either the placebo or 400 µg OTFC (all p-values ≤0.04). There was no statistical difference in difference between patients in 400 µg and placebo groups. The efficacy was consistent across the two centers and all administration periods.

Table II.2.6 Repeated Measurement Analysis of Morphine Usage

P-values of factors in Analysis of Repeated Measurements ANOVA							
	Treatment (T)	Center ©	T*C	Administration (A)	Interaction		
					A*T	A*C	A*C*T
Overall (Difference among all three groups)	0.03	0.008	0.92	<0.001	0.26	0.054	0.51
400 µg vs Placebo	0.73	0.011	0.66	<0.001	0.38	0.09	0.21
800µg vs Placebo	0.02	0.03	0.79	<0.001	0.27	0.10	0.58
800µg vs. 400µg	0.04	0.07	0.93	<0.001	0.20	0.15	0.71

Morphine equivalency -

Calculation of morphine equivalence was made by taken the difference of morphine use between

OTFC dose and placebo groups and divided by the amount of morphine use of OTFC group. The results were inconsistent in patients received 400 μg OTFC. As is shown in the following table, patients taking 400 μg OTFC in the center received more morphine than the patients in placebo group in the first and the fourth administration periods. In the center, patients taken 400 μg OTFC received more morphine than the patients in placebo group in the third administrative period. A possible explanation is that the inconsistencies were due to the intraoperative medications recieved by patients in the first administration period and low need of morphine in the third and fourth administration because of reduced pain.

Table II.2.7 Morphine Equivalency (patients evaluable for Efficacy at each Administration Period)

Administration Period	Placebo vs. 400 μg			Placebo vs. 800μg		
	Utah	Duke	Total	Utah	Duke	Total
1	-5.9*	3.1	-1.4	3.5	8.4	6.0
2	2.6	5.1	3.9	2.8	6.8	4.8
3	0.8	-0.4	0.2	2.1	1.3	1.7
4	-4.8	2.5	-1.1	1.0	4.2	2.6

*: (Morphine use in Placebo group - Morphine in OTFC group)/(Morphine use in OTFC group)

Visual Analog Score (VAS) -

Mean VAS was consistently lower in patients taken 800 μg OTFC than the other two groups and lower in patients taken 400 μg OTFC than those of the placebo groups in all administration periods. The differences were statistically significant in the second administration period between 800 μg OTFC group and 400 μg OTFC and placebo groups. There was statistically significant interaction between treatment and time. It was contributed by the increasing differences between 800 μg OTFC and 400 μg or placebo groups with time in administration period. The p-value of each factor in the ANOVA with repeated measurements are given in the following table.