effective as other potent opioid analgesics used for this indication. Moreover, because of the transmucosal route of administration, Actiq demonstrates a more rapid onset of action, within 15 minutes, compared to other oral agents which require gastrointesinal absorption in order to arrive at their effective systemic concentration. In a small number of patients (AC200/014), long-term use of Actiq continued to be effective at the same dose; however, firm conclusions regarding the development of dose tolerance are limited by the small number of patients in the long-term series.

9.0 Safety Findings

Acute postoperative patients were potentially those subjects with the greatest susceptibility to the most serious adverse effect of fentanyl, respiratory depression. In this opiate-naive population there were clinically significant episodes of respiratory depression and oxyhemoglobin desaturation observed in 21/92 subjects (23%). While it may be suggested that the high incidence of respiratory depression after OTFC was influenced by the concurrent use of intravenous morphine for analgesia, respiratory depression was also observed in the healthy non-premedicated volunteers who participated in the bioequivalence and pharmacokinetic studies (AC200/005, 006, 008, 009, 400/001). In these studies, 16/48 (33%) experienced desaturation, and of 12 patients in whom arterial blood gases were measured, 9 (75%) were hypercarbic. For this reason, the sponsor does not propose the indication of postoperative analgesia for Actiq. When assessing the potential risk of respiratory depression in the case of accidental ingestion, there is potential for serious overdose in children at even the lowest dosage units, based on the study experience with Fentanyl Oralet (NDA_ reproduced below (only pediatric patients are reported):

- Apnea: 2 cases
  age 3; 12 kg; 361 μg dose (30 μg/kg)
  age 3; 14 kg; 300 μg dose (22 μg/kg)

- Desaturation: 18 cases
  ages 2-9 yrs; dosage range 12-23 μg/kg

- Hypoventilation: 5 cases
  ages 5-7 years; 200-600 μg (14-25 μg/kg)

As may be seen from this data, unit doses in the lowest dosage range of Actiq (200-400 μg) in adults can represent a weight-based dose approximately 4-5 times the therapeutic dose in young children. The use of Fentanyl Oralet has currently been associated with a good safety experience, due to the administration of this product in a monitored in-hospital environment supervised by anesthesiologists or other physicians with training in assessment of sedation and

airway patency.

In the acute postoperative analgesia studies, other serious adverse effects which prolonged hospitalization (e.g., infection, ileus) were referable to the surgery that was performed. Other adverse effects experienced by the opioid-naive population are typical of fentanyl, morphine and other drugs in this class by all routes of administration, namely, pruritis, headache, nausea, vomiting, dizziness and somnolence.

The subjects of the dose-titration placebo controlled trial and long-term open-label study, as already indicated, were tolerant of chronic opioid therapy, and were able to use Actiq safely in an unmonitored environment. The type of adverse effects reported in the controlled clinical trials and the open-label uncontrolled trials are typical of mu-receptor opioid agonists. Adverse events that were grounds for withdrawal and also considered to be related to the use of Actiq in patients in the controlled and uncontrolled studies chronic pain studies combined, excluding deaths, are summarized in Table 12. The designation of an adverse event as related to Actiq has been determined almost entirely on the basis of the investigator's interpretation of the patients' diary entries, and specifically whether a temporal relationship could be established between the use of Actiq and the onset of symptoms. Overall, in the long-term safety study (n=155), there were 149 patients who had adverse events (96.1%), of which 53 (34.2%) were ascribed a relationship to treatment. Moderate + serious adverse events were 143 (92.3%), of which 30 (19.4%) were treatment-related, and serious adverse events were seen in 86 (55.5%) cases, of which 5 (3.2%) were treatment-related. Serious adverse events were generally of an organic nature, related to the patients underlying disease. Examples include thrombocytopenia, pathologic fracture, respiratory failure, infection, and pneumonia. The Sponsor's table of serious adverse events is included in the Appendix.

The most common significant adverse events (drug-related) were:

Controlled Clinical Trials (n = 257)		Open-label Trials (n = 155)
Somnolence	42	14
Dizziness	37	13
Nausea	29	12
Vomiting	11	8
Confusion	7	1
Hallucination	6	----
Asthenia	6	4
Abnormal gait/vertigo	4	----
Accidental injuries	2	----
Dyspnea	----	4

Myoclonus	----	2
Headache	----	1
Tachycardia	----	1

Respiratory depression was not reported in any patients in the chronic pain population, and there were no cases of apnea. The possibility should be considered that some episodes of agitation, confusion, hallucinations, and "abnormal thinking" may represent manifestations of hypoxia. In addition, the pharmacodynamics of fentanyl would suggest that episodes of somnolence would also likely be associated with some degree of respiratory depression. A few plasma levels of fentanyl were obtained in an attempt to correlate plasma fentanyl concentrations with serious adverse events. When obtained, plasma fentanyl concentrations were either subtherapeutic, or reflected the simultaneous absorption of transdermal fentanyl.

Four cases of dyspnea were reported in chronic pain patients. Dyspnea is an uncharacteristic side effect of potent opioids. However, chest wall rigidity has been reported with intravenous fentanyl, related to dose and rapidity of administration. One case of chest wall rigidity has been ferorted with premedication with Fentanyl Oralet, but at the time of loss of consciousness during induction with other agents. In awake individuals who can report the subjective feeling of dyspnea, therefore, chest wall hypertonia is an unlikely explanation. Another possibility for feelings of dyspnea might be an unmonitored cardiovascular effect.

Table 12. Withdrawals Due to an Adverse Event Considered to be Possibly, Probably, or Definitely Drug-Related, AC200/011, 012, 013, 014

Maximum Unit Dose	Study	Pt ID	Age	Gender	Reason for Withdrawal
200	200/012	21211	65	M	shortness of breath, chest pains, disorientation, unsteady gait, weakness
200	200/013	32508	61	F	itching,urticaria
200	200/013	32603	59	F	nausea
200	200/013	33503	69	F	nausea, lightheadedness, fatigue
200	200/013	33607	20	M	nausea
200	200/012	21212	75	M	dizziness, blurred vision, flushing
200	200/013	33002	78	F	vomiting
200	200/014	4604	57	F	itching, rash

400	*200/012*	*2408*	*45*	*F*	*nausea, vomiting,dehydration,weakness**
400	*200/012*	*21207*	*78*	*F*	*exacerbation of anxiety, abnormal vision, nausea**
400	200/013	33203	60	F	hallucinations, thinking abnormal, confusion
400	200/011	1106	46	F	Dry mouth, headache, dizzinss, sedation
400	200/014	42211	78	F	mouth sores
600	*200/012*	*21210*	*42*	*M*	*nausea, vomiting**
600	200/011	1205	54	M	nausea, vomiting
600	200/013	32210	71	M	nausea
600	200/011	1604	64	F	dizziness,hallucination,body numbness
600	200/014	4201	47	M	nausea, vomiting
800	200/013	32910	57	F	dyspnea, dizziness, sweating, weakness, anxiety
800	200/014	4202	55	F	*night sweats**, dizziness
800	200/014	41102	38	F	nausea
1200	200/014	42603	46	M	nausea, vomiting
1600	200/013	33802	51	F	nausea, vomiting, diarrhea, dehydration
1600	200/011	1208	61	M	inadequate pain relief, sedation
1600	200/013	33814	42	F	dizziness,confusion
1600	*200/014*	*43602*	*25*	*F*	*headache, confusion, agitation, nausea, vomiting**

* entries in *italics* were considered by the investigator to be unrelated to drug-use, but considered by the reviewer to be at least possibly related.

9.1 Deaths

There were no deaths in the bioequivalence, pharmacokinetic, or postoperative study population.

In the controlled clinical trials and the open-label uncontrolled trial there were no deaths that were directly attributable to the use of Actiq. Deaths were identified by the investigators as progression of underlying disease, usually after patients were readmitted to the hospital and Actiq had been discontinued for >24 hours. In

the controlled clinical trials the death rate was 4.3% (11/257). One patient's death was judged to have been possibly related to the use of Actiq, based on the use of Actiq within 1 ½ hours of death due to respiratory failure. The narrative for that patient is provided in the Appendix. In the reviewer's opinion, the use of Actiq did not contributed to the patient's death from his underlying disease.

At the time of filing of the NDA, the uncontrolled open label trial had a death rate of 26% (25/94). As of the November, 1996 safety update, there were 40 deaths out of 155 participants (25.8%). These deaths were the result of progressive disease. Summaries are provided in the Appendix.

9.2 Overdose Experience

There was one case of overdose which occurred in the open-label trial. An 85 kg, 75 year old male, was prescribed for 200 μg/unit and was also using 75 μg/day of transdermal fentanyl, which was increased to 100 μg/day later in the course of his participation. Due to a pharmacy error, he received a supply of 1600 μg/dose units, which he used for 9 days until the error was discovered. The patient was reported to have behavioral changes, considered by the investigator to be unrelated to the dose of Actiq, but the likelihood that there was a relationship is equally, if not more plausible.

9.3 Significant/Potentially Significant Events Considered Possibly/Probably/ Definitely Drug-Related

None

9.4 Other Significant Events Considered Not Drug-Related

None

9.5.2 Laboratory Findings

Clinical laboratory evaluations were performed in chronic pain patients in two studies, AC200/011 and AC200/012 and in normal volunteers in the pharmacokinetics study AC200/005. The number of patients who demonstrated changes from normal values was provided by the Sponsor in Tables 5-1 and 5-2 in the Sponsor's Integrated Summary of Safety. Changes of biochemistry variables from normal to abnormal values in both directions, and, in some cases, from abnormal to normal values, were observed during the course of the study period. No consistent deviations of any particular assay were seen, tending to support these observed changes as being more likely related to underlying subjects' state of health, rather than the effect of Actiq. Table 13 presents a summary of the frequency of deviations from normal values for the major biochemical variables that

were assayed before and after Actiq use.

Elevations of post-trial liver function tests were seen in 25/127 (19.7%) chronic pain patients, compared to pretrial values, and 20/127 (15.8%) had pretrial elevated liver function tests which fell to normal values post-trial. Seventy-one patients had elevation of one or more liver enzymes at the time of entry into the study, which remained elevated at the time of exit. Normal volunteers showed no changes in biochemistry results. A minority of chronic patients showed changes of hemoglobin or hematocrit (5 patients increased to normal, 5 patients decreased). The leukocyte count rose in 11 patients, fell to normal in 5 patients, and fell to below normal in 5. Five normal volunteers demonstrated a fall in hemoglobin and hematocrit, suggested by the sponsor to possibly be due to the amount of blood sampling performed for the pharmacokinetic study (approximately 150 ml). It is pertinent to note that chronic pain patients in AC200/011 and AC 200/012 participated for a 20 day duration, and normal volunteers participated for 24-48 hours.

Table 13. Summary of Clinical Laboratory Results. Number of Patients with Post-trial Values Within and Outside of the Normal Ranges.

Laboratory test	Chronic pain patients (n=127)			Normal Volunteers (n= 12)		
	normal	elevated	below	normal	elevated	below
Albumin	86	0	8	12	0	0
Alk Phos	61	33	0	12	0	0
ALT (SGPT)	89	5	0	12	0	0
AST (SGOT)	86	8	0	12	0	0
Bilirubin (total)	91	3	0	12	0	0
GGT	62	32	0	12	0	0
LDH	79	15	0	12	0	0
Creatinine	77	6	10	12	0	0
BUN	82	4	8	12	0	0
Glucose	65	22	7	10	2	0
Hemoglobin	29	0	56	5	0	7
Hematocrit	32	0	63	2	0	10
WBC	73	8	14	10	1	1
Platelets	77	7	11	12	0	0

9.5.3 Vital Signs

The combined incidence of cardiovascular related effects of all causality on chronic pain patients (n=257) were: 0% (n=0) for bradycardia, 1.6% (n=1) for tachycardia, 1.6% (n=4) for hypotension, and 1.2% (n=3) for hypertension. Of these, one episode of tachycardia was considered to be possibly related to Actiq. Fentanyl is not associated with negative inotropic or vasodepressor effects; sinus bradycardia which may be seen in anesthetized individuals is characteristic of potent opioids, but is not seen in awake or opioid tolerant individuals.

9.5.4 ECGs

Electrocardiographic monitoring was not used in these studies, as there is no described arrhythmogenic potential associated with fentanyl.

9.5.5 Special Studies

None

9.5.6 Drug-Demographic Interactions

Age-related safety differences were examined by comparing treatment-related adverse events in patients <65 vs >65 years. There were no significant differences demonstrated by this comparison.

Gender- related differences were similarly examined, and there were found to be no statistically significant differences between males and females for treatment-related adverse effects.

9.5.7 Drug-Disease Interactions

The pathophysiology of each patient's persistent pain and breakthrough pain was classified into categories as follows: 1) nociceptive-somatic, 2) nociceptive-visceral, 3) neuropathic, 4) other. The Sponsor examined the incidence of treatment-related side effects between groups characterized by type of pain. Table 14 reproduces table 10-6 of the Sponsor's Integrated Summary of Safety, using patients in the open-label safety trial.

Table 14. Patient Number and (%) with Treatment-related Adverse Effects, vs Predominant Pain Pathophysiology (AC200/014)

	Neuropathic n=22	Nociceptive-Somatic n=50	Nociceptive-Visceral n=22	p-value[a]	Rel. Risk neuro: noci. Total	95% Conf. Limits	
						Lower	Upper
Somnolence	4 (18.2)	5 (10.0)	1 (4.5)	0.2362	2.1818	0.6761	7.0410
Nausea	2 (9.1)	4 (8.0)	1 (4.5)	0.6642	1.3091	0.2727	6.2846
Constipation	2 (9.1)	3 (6.0)	1 (4.5)	0.6220	1.6364	0.3210	8.3421
Vomiting	0 (0)	3 (6.0)	0 (0)	1.0000	–	–	–
Dizziness	7 (31.8)	2 (4.0)	0 (0)	0.0004	11.455	2.5631	51.191
Asthenia	0 (0)	1 (2.0)	0 (0)	1.0000	–	–	–
Headache	0 (0)	1 (2.0)	0 (0)	1.0000	–	–	–
Rash	0 (0)	1 (2.0)	0 (0)	1.0000	–	–	–
Pruritis	0 (0)	1 (2.0)	0 (0)	1.0000	–	–	–
Dry Mouth	0 (0)	1 (2.0)	0 (0)	1.0000	–	–	–
Confusion	0 (0)	0 (0)	0 (0)	–	–	–	–
Sweating	1 (4.5)	0 (0)	0 (0)	0.2340	–	–	–
Nervousness	1 (4.5)	0 (0)	0 (0)	0.2340	–	–	–
Any[b]	10 (45.5)	15 (30.0)	2 (9.1)	0.6642	0.9769	0.8439	1.1310

[a]Fisher's exact test (2-tailed); [b]other side effects not attributed to treatment relationship

Treatment-related adverse effects were seen at a significantly higher incidence in patients with neuropathic pain compared to nociceptive pain ($p < 0.05$), and this difference was identified as due to a higher incidence of dizziness in patients with neuropathic pain ($p = 0.0005$). Other adverse effects which might be attributed to disease rather than treatment were not different between patients with nociceptive vs neuropathic pain.

9.5.8 Drug-Drug Interactions

Patients in the chronic pain studies were taking multiple medications which include other opioid analgesics, non-opioid analgesics, corticosteroids, antidepressants, chemotherapeutic agents, and antibiotics, among others. The sponsor indicated (ISS, section 9.2 - data not presented) that there was no difference in adverse effects between patients who were simultaneously taking drugs known to interfere with hepatic microsomal activity and those who were not. The mean total dose of Actiq per episode was 1115 μg for patients taking microsomal substrates or inhibitors, compared to 1121 μg for patients not taking these agents, a non-significant difference ($p = 0.97$). These observations are

consistent with the high hepatic clearance of fentanyl, which is dependent on hepatic blood flow, but insignificantly affected by microsomal enzyme inducers or inhibitors. Hepatic failure, however, is known to effect elimination kinetics of fentanyl.

9.5.9 Withdrawal Phenomena/Abuse Potential

At the present time, fentanyl in all its formulations is classified as a C II narcotic; distribution of oral transmucosal fentanyl, as Fentanyl Oralet, has been restricted to in-hospital use under appropriate supervision of specialty-trained personnel. Distribution and record-keeping of Fentanyl Oralet has been subject to meeting accredited policies for handling of controlled substances and intra-institutional policies which tightly control distribution. Actiq is intended for release out of the hospital environment, and has been demonstrated to be safely and appropriately used under the terms of this clinical development program. Nevertheless, there is a potential for inadvertent overdose, both due to the identical appearance of all dosage strengths, and ease of use (for instance, by children) once the lozenge has been removed from the package. Diversion of intravenous fentanyl for abuse has been a factor primarily among hospital personnel who have access to it. With regard to Actiq, possible diversion for abuse should be considered higher than for intravenous fentanyl due to the portability of the dosage form and the palatability of the pharmaceutical preparation.

Problems of potential inadvertent overdose and diversion for abuse which need to be addressed by the sponsor are:

- Fentanyl has been abused by transdermal patch. Willingness of drug-abusers to ingest fentanyl, even in unpalatable form (e.g. ingesting the gel of a transdermal patch) makes the expectation of abuse of a palatable oral form reasonable.The clinical studies demonstrate that all dosage strengths deliver effective blood fentanyl concentrations, with onset of action at 5-10 minutes from the completion of ingestion.

- The size of individual lozenges makes it feasible to use multiple units simultaneously. According to data presented in the Abuse Liability Review, a maximal dose of 8 mg fentanyl citrate in 15 minutes is possible (5 units, 1600 μg per unit). However, absorption across other mucosal surfaces for the purpose of achieving a higher blood level has not been evaluated.

- In the current product (Fentanyl Oralet), the drug lozenge is attached to a flat paddle which identifies the dosage strength. The shape of the paddle was devised in order to minimize the possibility of accidental swallowing (or aspiration). As Actiq, the drug lozenges look identical despite an eight-fold difference between the lowest and the highest unit dose. Consideration

should be given to distinguishing coloring and marking characteristics of the drug matrix, handle and outer packaging. Repetitive warning labeling for the case, box, and unit packages should emphasize dosage strength, warning information, and disposal instructions. Fentanyl Oralet units are also encased in individual clear plastic containers with a "snap-lock" type of fitting, which should be retained for Actiq to enhance safety from accidental access by children.

In summary,, while the product has been demonstrated to have acceptable efficacy, safety, and low potential for abuse in the target population, cancer patients with chronic pain, the risk management plan must address the possibility of diversion for abuse, misuse, and accidental toxicity in children, and drug abusers.

10.0 Labeling Review

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11.0 Conclusions

The Sponsor's clinical development plan supports the indication of Actiq for the outpatient treatment of breakthrough pain in opioid tolerant patients who are stable on long-acting opioid analgesics for chronic pain. The sponsor's model for individual titration from the lowest unit dose strength of Actiq (200 μg) up to the effective unit dose is reasonable from the standpoints of ease of patient compliance and safety because:

- A predictable relationship between around-the-clock opioid dose and effective Actiq dose could not be established.

- Common opioid related side effects (e.g. nausea, pruritis) do not demonstrate a dose-dependent relationship, while respiratory depression does.

- 32% of patients (29/91) in the open label uncontrolled trial continued to use

the two lowest dosage strengths throughout their participation.

- Safety is enhanced by using the entire lozenge to achieve effective analgesia, rather than by partial or intermittent use of more potent units.

At the effective dose, Actiq appears to be at least as effective as other potent opioid analgesics used for this indication. Moreover, because of the transmucosal route of administration, Actiq demonstrates a more rapid onset of action, less than 15 minutes, compared to other oral agents which require gastrointestinal absorption in order to arrive at their effective systemic concentration. In patients followed for up to one year with long-term use of Actiq, the same dose continued to be effective over time; however, firm conclusions regarding the development of dose tolerance are limited by the small number of patients in the long-term series.

The use of Actiq for postoperative analgesia was investigated in two opiate-naive groups, one who received no other analgesics and another who were also receiving morphine PCA. In both groups Actiq in an effective dose was associated with an unacceptably high incidence of ventilatory depression. The use of Actiq for this indication is not recommended, and patients who are not tolerant to opiates should not receive Actiq in an unmonitored environment.

The risk management plan will include DEA regulations and surveillance required under classification as a class C II narcotic, and must also address issues of safety in labeling, packaging, education and control of distribution. Items already discussed with the Sponsor include:

- Conspicuous dose identification on the unit handle.
- Color identification of different dosage strengths.
- Redundant label warnings regarding appropriate patient use, child safety warnings, and disposal instructions on individual unit pouches and cartons.
- Child-proof packaging design.
- Explicit and conspicuous child safety and disposal warnings in the patient package insert.
- Education programs and materials (physicians, pharmacists, 800 number) to define appropriate patient selection and discourage inappropriate use
- Pharmacist role to determine appropriateness of prescription at the time of dispensing.
- Toxic exposure surveillance, surveillance of Poison Control Centers, and prescription surveillance.

12.0 Recommendations

Actiq should be recommended as approvable for the indication of the

treatment of breakthrough pain in cancer patients with chronic pain who require and are tolerant to the effects of potent opioid medications. The dosage range of 200, 400, 600, 800, 1200 and 1600 μg/ unit, allowing individual titration to the effective analgesic dose is justified by the experince presented in the clinical development plan.

The plan to address the risk management issues is in development between the Agency and the Sponsor.

DIV H.

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

MAY 16 1997

MEDICAL OFFICER CLINICAL STUDY REVIEW

NDA: 20-747

Product: Oral Transmucosal Fentanyl Citrate (OTFC)
Sponsor: Anesta Corp.

Submission: Commercial/ Study Summary Report
Protocol #: AC 200/012

Title: A Dose Titration, Multicenter Study of Oral Transmucosal Fentanyl Citrate(OTFC) for the Treatment of Breakthrough Pain in Cancer Patients Using Transdermal Fentanyl

Date of Review: 5/8/97

Project Manager: M. Wright
Medical Reviewer: Roberta C. Kahn, M.D.

Background

Oral Transmucosal Fentanyl Citrate (OTFC) is a preparation of fentanyl citrate, a potent narcotic analgesic, in a sucrose/glucose/flavor base for oral transmucosal ingestion. This study is part of a clinical plan presented in support of this NDA for the indication of OTFC (Actiq) use for the treatment of cancer patients who are receiving chronic narcotic analgesic therapy as a transdermal fentanyl patch.

Clinical Study

This was a randomized, double-blind dose titration study of 200-1600 μg OTFC, conducted in 11 centers geographically dispersed throughout the United States. The objectives of this study were:

- to evaluate the safety and efficacy of OTFC as a treatment for breakthrough pain in cancer patients taking scheduled doses of transdermal fentanyl
- through a titration process, to demonstrate that a single unit dose of OTFC could control episodes of breakthrough pain.

Subjects: 62 cancer patients, ages 25-91 years, using around-the-

clock transdermal fentanyl (50-300μg/hr) for pain associated with their disease and having on average 1-4 episodes/day of breakthrough pain were recruited. Patients who had more than one type or location of pain were asked to identify one as their "target" pain.

Randomization/ Blinding: After informed consent, patients were randomized to receive 200μg or 400μg as a starting dose. An exception was made in patients who routinely used < 100μg/hr of transdermal fentanyl; these patients were always assigned to start at 200μg OTFC. Dose titration occurred in a blinded fashion through successive doses of 600, 800, 1200 and 1600μg/unit. Neither the investigator nor the patient was aware of the dose. The dispensing unblinded pharmacist was instructed to ignore the dose increase 1/3 of the time, according to a sponsor-supplied randomization schedule.

Clinical Plan: The study was divided into a Baseline Phase, a two-day collection of data in which the nature and severity of the patient's breakthrough pain and the performance of his/her regular rescue medication was evaluated. Next the patient entered participate in the OTFC Phase, the dose titration phase for up to 20 days. The primary aim of the study was to compare the two days of baseline data with two days of OTFC data, once the effective dose had been identified.

At entry into the OTFC phase, the patient received the initial blinded OTFC dose for the onset of breakthrough pain. For each episode, the patient scored pain intensity (PI) on a 0-10 scale immediately prior to the dose and every 15 minutes after OTFC for one hour. After complete ingestion of OTFC, pain relief (PR) was scored on a 0-4 scale every 15 minutes for one hour. If the pain was not relieved within 15 minutes from onset, an additional unit of OTFC at the same dose could be taken, up to a total of 4 units per episode. The patient also gave a global performance rating (scale 0=poor to 4=excellent) for the OTFC dose at the end of each treatment day.

Two episodes per day were treated. To increase safety, only breakthrough episodes occurring between 7 am and 4 pm were treated. At the next clinic visit, the investigator decided whether the patient required an increase or decrease to the next available (blinded) dose. Dose titration continued until 2 successive days of successful treatment with a single dose of OTFC were achieved. A maximum of 20 days were allowed for titration. Patients who could not achieve satisfactory pain relief with the 1600μg dose were considered failures of therapy. Withdrawals for adverse effects were recorded.

Amendment Protocols:

Amendment 1 was added prior to the study start. Under this amendment the starting dose was randomized and blinded. If the randomly assigned dose was > 20% of the patient's 24 hr transdermal fentanyl dose, the patient was assigned to 200 μg. Other stipulations of this amendment: exclusion of patients who had received Strontium 89 therapy, extending the study period from 15 to 20 days, and requiring that use of adjuvant analgesic therapy be maintained on a fixed schedule.

Amendment 2 allowed for additional study centers and the deletion of the projected completion date.

Amendment 3 allowed patients with swallowing dysfunction to participate, as long as they could effectively administer the OTFC, and allowed patients who had to discontinue participation because of an unforeseen medical complications to re-enroll after resolution and stabilization.

Variables:
Primary Efficacy Variables: pain intensity (PI), pain relief (PR), global performance of OTFC and regular rescue medication.

Secondary Efficacy Variables: mean effective dose of OTFC.

Safety Variables: adverse events within study period.

Statistical Analysis:
Pain Intensity (PI), Pain Intensity Difference (PID), and Pain Relief (PR) and were calculated for each patient episode at each time point. The mean for each variable for the baseline phase and the OTFC phase were compared statistically. Efficacy variables measured at a single time point were averaged and compared between the baseline and OTFC phases.

Two-way ANOVA included terms for treatment group (200 vs 400μg starting dose), treatment center, and group by center for: around-the-clock dose, PI, PID, PR, global performance of each analgesic, number of target episodes/day, number of increases of OTFC dose, and final OTFC dose.

Two-way ANOVA included terms for nociceptive (somatic + visceral) vs. neuropathic for: around-the-clock dose, regular rescue dose, ratio ATC/rescue dose.

Linear regression for: regular rescue with ATC dose as independent variable, final OTFC dose with ATC dose as independent variable, and final OTFC dose with regular rescue as independent variable.

Covariance analysis for final OTFC dose vs. regular rescue dose.

Paired t-test for within-patient comparisons of primary efficacy variables at all time points, for 1) baseline, 2) OTFC, 3)baseline vs. successful OTFC days, 4) first vs. last OTFC dose.

Additional two-way ANOVA for between-center comparisons, and comparisons between nociceptive vs. neuropathic pain. Three-way ANOVA which included terms for investigator, subject within investigator, phase, investigator by phase interaction was also performed for pain intensity, pain intensity difference, pain relief, and global performance.

Three-way ANOVA for efficacy variables with terms included for investigator, subject within investigator, phase, investigator by phase interaction.

Fisher's Exact test for completion status, gender, race, global performance of regular rescue vs. failure at 1600μg.

One-way ANOVA, with a term for starting OTFC dose, for: final successful OTFC dose, 90% confidence interval for between-treatment differences of efficacy variables at all time points. For final OTFC dose, a final dose of 200μg was taken as 400μg for statistical analysis.

One-way ANOVA, with a term for exit code status, for all efficacy variables for the baseline phase.

Exact binomial confidence interval for each COSTART adverse event. 90% upper confidence bound was calculated using exact binomial distribution.

Patients who were assigned to the 200μg starting dose were excluded from statistical analysis because they were not part of the randomization protocol.

Results

The mean age of patients randomized to 200μg was 54 $\pm$ 12 years and 62 $\pm$ 16 years for patients randomized to 400μg, and this difference was significant. There were no other significant differences between demographic variables. There were also no differences in baseline pain severity scores between randomized treatment groups. When regular rescue medications were converted to morphine-equivalent, patients randomized to the 400μg starting dose had a significantly higher rescue dose, 39 $\pm$ 29 mg morphine-equivalent (mean $\pm$ SD), compared to patients randomized to 200μg, 20 $\pm$ 17 mg morphine-equivalent.

Table 1 (see below) presents the distribution of patients in all treatment groups: assigned to 200μg starting dose, randomized to 200μg starting dose, and randomized to 400μg starting dose.

Table 1 (based on Sponsor's Table 8) Number of patients at each starting dose and completion status

Patient Status	Assigned to 200μg n (%)	Randomized to 200μg starting dose n (%)	Randomized to 400μg starting dose n (%)	Total n (%)
consumed OTFC	33	18	11	62
completed 2 successful days	26(79%)	13(72%)	8(73%)	47(76%)
withdrew: adverse event	3(9%)	1(6%)	2(18%)	6(10%)
failure at 1600μg	1(3%)	3(17%)	0(0%)	4(6%)
other withdrawal	3(9%)	1(6%)	1(9%)	5(8%)

p = 0.54 by Fischer's Exact test for completion status, between patients randomized to 200 vs. 400μg.

13/18 patients randomized to start at 200μg and 8/11 patients randomized to start at 400μg achieved successful pain relief under the terms of the protocol. In addition, 26/33 patients who were not randomized and were all started at 200μg achieved successful pain relief. For the group randomized to 200μg, the mean effective dose was 677 ± 466μg (mean±SD), compared to 825 ± 345μg for the group started at 400μg. The mean effective dose for the non-randomized treatment group was 469 ± 178μg. The 90% confidence interval for the ratio of the 200 and 400μg doses was 50% to 109%. This confidence interval does not support equivalency for the mean final doses in the two randomized groups. Comparing randomized patients only, the difference between the mean effective doses were not statistically significant by two-way ANOVA with factors for starting dose, for center, and for treatment-by-center interactions. It is important to note that:

1) patients not randomized were excluded from statistical analysis, making the two sample sizes small, and

2) for computing mean, SD, SEM, and statistical analysis patients whose final dose was 200μg were combined with patients whose final dose was 400μg.

During the dose titration phase, one third of orders to increase OTFC were ignored according to a randomization schedule. 14/47 successful patients had increase orders ignored 18 times. Of those times, only 9 were unsuccessful at the same dose, and required titration to a higher dose.

Linear regressions were performed between the regular rescue medication vs. around-the-clock fentanyl, and final OTFC dose vs.

around-the-clock transdermal fentanyl. The slope of the regression was statistically significant ($p = 0.0004$), but the causation coefficient was low ($r^2 = 22\%$). The results of linear regression for OTFC vs. around-the-clock transdermal fentanyl were similar: p value = 0.002, $r^2 = 19\%$.

Comparisons between OTFC and the patients' regular rescue medication indicate a shorter onset and shorter duration of action of OTFC compared to regular rescue. Table 2 reproduces this data for all patients who achieved successful analgesia with OTFC (n = 47).

Table 2. Mean PID and PR Scores: Regular Rescue vs. OTFC (Adapted from Sponsor table 28)

Variable	Number	Rescue Score at Baseline	OTFC, Successful Day	p value*
PID: 0-15 min	40	0.91	2.35	0.0001
15-30 min	39	1.14	1.38	0.33
30-60 min	43	1.27	0.61	0.0001
Total PID		3.32	4.34	
PR: at 15 min	40	0.82	1.90	0.0001
15-30 min	39	0.75	0.54	0.13
30-60 min	43	0.74	0.41	0.005
Total PR		2.31	2.85	

* paired t-test

The table indicates that onset of analgesia after OTFC occurs within 15 minutes of ingestion, due to the transmucosal route and lack of first-pass effect, and is significantly faster than standard oral opioids used for breakthrough pain. By the 30 minute interval, the analgesia provided by both therapies is comparable. For the study interval between 30 and 60 minutes, the effect of regular medications is sustained, while the effect of OTFC is dissipating; the difference in pain scoring variables at this measurement interval again becomes highly significant.

The mean Global Performance rating for OTFC was 2.68, compared to 2.01 for regular rescue. This difference was not statistically significant by two-way ANOVA, with factors for starting OTFC dose, treatment center, and treatment dose-by-center. There was also no difference between the two starting doses of OTFC compared to each other. In the nonrandomized group who were assigned a starting dose of 200μg, Global Performance with OTFC was 2.71, compared to 1.68 for regular rescue. According to the terms of the study design, no statistics were done on variables

from the assigned group.

TREATMENT FAILURES AND ADVERSE EVENTS

Four patients were unable to find an effective dose of OTFC, up to a unit dose of 1600μg. Two patients' pain was characterized as nociceptive, and two as neuropathic. One patient experienced nausea, vomiting and dizziness; 1 experienced somnolence, 1 experienced constipation/diarrhea, 1 reported brief (1 min) shortness of breath.

Six patients withdrew due to adverse events, and 5 patients withdrew for other reasons.
Three withdrawals were for adverse effects related to the study medication.

1. (pt ID# 21211) dyspnea, chest pain, disorientation, unsteady gait, weakness (200μg)
2. (pt ID# 21212) dizziness, blurred vision, flushing (200μg)
3. (pt ID# 21207) nausea, anxiety, abnormal vision. (400μg); (only nausea considered by investigator to be related AE)

Other withdrawals due to adverse events:

4. (pt ID# 21201) increasing pain (200μg)
5. (pt ID# 21210) nausea, vomiting(200μg)
6. (pt ID# 2408) nausea, vomiting, dehydration, weakness (400μg)

Other reasons for withdrawal were inability to comply with study protocol (3 cases), inability to consume OTFC (1), and inadequate pain relief (1).

The most common adverse events related to the study drug are listed. This list relies on the rating of the investigator as to whether the adverse event was related or unrelated to the study drug. The total incidence is the sum of cases judged to be "related" + cases judged to be "unrelated," listed in parentheses.

1. Somnolence: 11
2. Nausea: 7 (+ 6 unrelated)
3. Dizziness: 6 (+ 3)
4. Vomiting: 3 (+ 5)
5. Constipation: 2 (+ 2)
6. Dyspepsia: 1 (+ 1)
7. Diarrhea: 1 (+ 3)
8. Dyspnea: 1 (+ 3)
9. Vasodilation, abnormal dreams, abnormal vision, pruritis (one report each): 4

There was one case of accidental injury on the last day of the study. The patient's OTFC dose was 600μg. The patient was admitted to a hospice for increasing weakness and loss of appetite, considered to be related to disease progression.

REVIEWER CONCLUSIONS

This study was designed to identify clinically effective and safe doses of oral transmucosal fentanyl citrate by titration through fixed unit dosage of OTFC, and compare their efficacy to standard oral opioids used by this patient population. 47/62 (76%) of patients in this study were able to arrive at a satisfactory single-unit dose of OTFC to control breakthrough pain episodes. The patients' assessments of pain control appeared to compare favorably to their experience with regular rescue medication. Onset of analgesia with OTFC was earlier compared to regular rescue medication, and appeared to dissipate sooner.

This study failed to demonstrate a close dose-response relationship for OTFC. The randomization protocol did not support equivalency of the final mean effective doses in the two randomized groups. Also, among patients who blindly received the same dose rather the expected next-higher dose for their next episode of breakthrough pain, 50% achieved satisfactory pain relief anyway.

Drug-associated adverse events that were observed are those characteristically associated with opioid medications. The study design did not include comparisons of side effects due to OTFC, as compared to regular rescue medication. The global assessment implies that this comparison is taken into account by the patient, but the Global Ratings of OTFC and regular rescue were not significantly different. The most prominent adverse effects were somnolence, nausea, and dizziness. Adverse effects occurred throughout the dose range, and were responsible for withdrawal from the study in 3 cases.

No firm conclusions can be drawn regarding adverse effects on pulmonary function. Respiratory monitoring was not performed in this study. Dyspnea was reported in 4 cases, of which 3 were considered unrelated to the study drug. Dyspnea is not a characteristic side effect of opioid agents; however, dyspnea may be a non-specific symptom of bronchoconstriction, chest wall rigidity, and negative cardiac inotropy, all of which are possible effects of fentanyl.

/S/ 5/16/97

Roberta C. Kahn. M.D. Date

/S/ 5/16/97

Peer Reviewer Date

NDA # 20-747
HFD-170/Div. File/ R. Kahn/ M. Wright
HFD-170/R.Kahn

Draft

MAY 16 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION of ANESTHETICS, CRITICAL CARE and ADDICTIVE DRUGS

REPORT ADDENDUM

IND: 20-747

Product: Actiq (Oral Transmucosal Fentanyl Citrate)
Sponsor: Anesta

Submission: commercial Protocol: AC 200-014 Amendment: 004
Title: An Open-Label, Long-term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other OTFC Studies.

Date of Review: May 1, 1997

Project Manager: M. Wright
Medical Reviewer: Roberta C. Kahn, M.D.

Summary
This study is submitted in support of NDA 20-747, with the new indication of OTFC as an outpatient treatment for breakthrough pain in an opioid-tolerant chronic cancer population. The study aim was to assess the long-term safety and tolerance of OTFC. Patients entered at a dose determined to be the effective dose during their participation in previous OTFC studies; however the dose could subsequently titrated as needed. Each enrollment block was 4 months, and patients could elect to re-enroll as long as they continued to experience breakthrough pain and could satisfy the study requirements for documentation of their medication use.

The study was conducted at 32 centers in the United States. Patients who successfully completed one of the previous clinical studies (AC200/011, 012, 013, 015) were eligible to enroll. The dose range of OTFC was 200, 400, 600, 800, 1200, and 1600 μg/unit.

In the final study report, the sponsors provided the Table 15, indicating the number of patients who remained at their initial dose and the number who titrated to another dose, either higher or lower.

Table 15. Initial OTFC Dose Level in Relation to Last OTFC Dose Level- All Patients Reported

Initial Dose(μg)	Patient Number at Each Last Dose						Pts. Finding 1600 μg ineffective*	Total No.
	200μg	400μg	600μg	800μg	1200μg	1600μg		
200	15	4	0	2	0	0	0	21
400	1	14	4	3	5	2	0	29
600	0	0	12	4	1	1	0	18
800	0	1	0	4	2	5	2	12
1200	0	0	0	0	3	1	0	4
1600	0	0	0	0	2	5	1	7
Total	16	19	16	13	13	14	3	91

*Patients in this column were also listed in the 1600 μg Last Dose column.

In the aggregate, 58% of patients remained at their initial effective dose throughout their participation. However, Table 15 does not consider time as a factor: do patients who remain the longest in the study require progressively higher doses? In order to better assess the possible development of tolerance, the sponsors were requested to provide a summary table of monthly patient number, with initial and final doses of OTFC for each monthly group. This amendment provides initial vs final dose level on a monthly basis in a series of tables, the contents of which will be summarized here.

Month 1: 91 patients were participating. 69/88 patients (78%) did not require an increase in their dose. 3 required a decrease, 1 from an initial dose of 400 μg, and 2 from an initial dose of 1600 μg.

Month 2: 65 patients were participating. 51/65 patients (78%) remained at their initial dose. No patient participating through this time period required a reduction of dosage. Only at the 1600 μg dose did no patient (n=5) require an increase.

Month 3: 50 patients were participating. 44/50 patients (88%) remained on their initial dose. No patients required reduction to a lower dose. Out of 24 patients receiving 600, 800, or 1200 μg/dose, only one patient at each dosage level required an increase to the next higher dose. None of 9 patients at 1600 μg changed their dose.

Month 4: 37 patients were participating. 34/37 patients (92%) remained at their initial dose. No patients at 200,1200, and 1600 μg changed their dose. 2 patients increased their dose once and 1 patient increased his dose twice.

There were 25 patients participating in months 5-8 and 10 patients participating during months 9-12. 5 of these 35 patients required an increase in dosage strength. 4 patients continued to be followed for >12 months. One of 2 patients at 600μg increased to 800 μg/dose. One patient at 1200 μg and one at 1600 μg/dose remained at these doses.