Discussion

Over the course of the observation time the highest frequency of dosage adjustments occurred early, during the first 2 months. Although there is a steady decline in participation with time, in general it appears that most patients were able to identify an effective dose which remained effective over time. The percentage of patients who remained at the same dose was 78% in the first 2 months and remained at 88-92% during subsequent time periods. The sponsor's tables also indicate that the entire dose range was still in use through Month 4; after that only one patient (Months 5-8) was using 200 μg/dose, but 6 patients were still using 400μg/dose through Months 9-12. Even in the latest time periods patients were not clustered around the highest dose available. The data suggests that tolerance to the analgesic effect of OTFC over time is manageable for most patients. Any influence due to adjustments of around-the-clock analgesics during the study period cannot be identified.

According to the protocol, downward adjustments of dosage were made in response to side effects. Only 3 patients required a dosage reduction, and all were in the first month of the trial; this observation tends to support the sponsor's statement that tolerance to side effects improves with time, and is consistent with experience with other opioid analgesics.

Conclusion

This addendum to AC 200/014 supports the sponsor's labeling claims that:

- Titration of the dose for breakthrough pain is a practical method of establishing the effective dose of OTFC for each patient.

- Early adjustments in dose may be necessary, for either efficacy or adverse effects, but for the majority of patients it is possible to identify a dose of OTFC that will be effective consistently over a long period.

/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

Appendix

List of Investigators

Dose-Response Relationships of Morphine/Actiq

Bioavailability Curves of Intravenous Fentanyl, OTFC, and Oral Fentanyl Solution

Table of Serious Adverse Events

Narratives of Hospitalizations and Deaths

Table 3. Center Description

Primary Investigator	Center	Center Number	Patient No.
Sites with Patients Included in Interim Analysis			
James Raschko[a], MD	City of Hope Medical Center, CA	1008	4101-4112
Richard Payne, MD	MD Anderson Cancer Center, TX	1010	4201-4208
Russell Portenoy, MD	Memorial Sloan-Kettering Cancer Cntr, NY	1012	4301-4311
Mary Simmonds, MD	Cowley Associates, PA	1009	4401-4410
Julia Smith, MD	University of Rochester Cancer Center, NY	1013	4501-4502
Eric Winer, MD	Duke University Medical Center, NC	1014	4601-4604
Alan Lyss, MD	Missouri Baptist Cancer Center, MO	1016	4701-4707
Michael Schuster, MD	North Shore University Hospital, NY	1021	4801
Arthur Staddon, MD	The Graduate Hospital, PA	1022	4901
Patricia Plezia, PharmD/ Manuel Modiano, MD	Arizona Clinical Research Center, AZ	1024	41001-41002
Lloyd Saberski[b], MD	Yale University, CT	1028	41101-41103
Joan M. Christie, MD	Hospice Institute of FL Suncoast, FL	1027	41201-41204, 41206-41208
Lowell Hart, MD	Associates in Hematology/Oncology, FL	1034	42201-42203, 42208
Janet Gargiulo, MD	Capital District Hemat/Oncol Assoc, NY	1033	42301-42302
Howard Homesley, MD	Baptist Hosp/Carolina Gyn Oncol, NC	1036	42502
Richard Rauck, MD	Bowman Gray School of Med, NC	1042	42601-42602
Kelly Pendergrass, MD	Kansas City Internal Medicine, MO	1041	42901-42904, 42906-42907
Lee Schwartzberg, MD	The West Clinic, TN	1044	43401
Mark Seligman, MD	Providence Med Cntr, OR	1045	43501
John Farrar, MD	University Pennsylvania Med Center, PA	1049	43601, 43604, 43610
Robert Berris, MD	Rocky Mountain Cancer Centers, CO	1051	43801, 43805, 43807
Robert Ellis, DO	Madigan Army Medical Center, WA	1059	44403-44404
William H. Whaley, MD	West Paces Medical Center, GA	1062	44701
Active Sites With No Patients Included in Interim Analysis[c]			
Allen Cohn, MD	Univ Colorado Health Sciences Cntr, CO	1053	–
James Cleary, MD	Univ of Wisconsin Hosp. & Clinics, WI	1046	–
Michael Gauthier, MD	University of Utah, UT	1055	–
Donna S. Zhukovsky, MD	The Cleveland Clinic Foundation, OH	1047	–
Gregory B. Smith, MD	Southwest Regional Cancer Center, TX	1058	–
John Marshall, MD	Georgetown Univ Hosp, DC	1038	–
K.S. Kumar, MD	New Port Richey, FL	1057	–
Laura Hutchins, MD	Arkansas Cancer Research Center, AR	1060	–
Timothy J. Ness, MD	University of Alabama-Birmingham, AL	1061	–

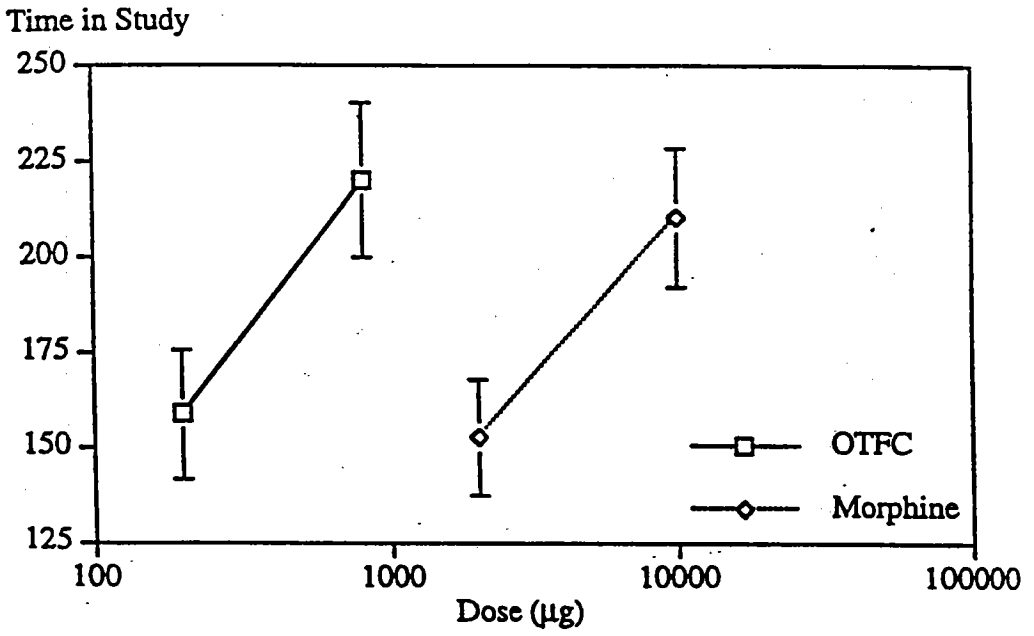
[a]Replaced Paul Coluzzi, MD, as principal investigator

[b]Replaced Ann Berger, MD, as principal investigator

[c]Active sites that did not have any patients complete at least 4 months or withdraw by July 15, 1996

Parallelism of High Dose (10 mg intravenous) Morphine to Low Dose (2 mg intravenous) Morphine with High Dose (800 μg) Oral Transmucosal Fentanyl Citrate to Low Dose (200 μg) Oral Transmucosal Fentanyl Citrate

Figure 6. Dose-Effect Curves of Time in Study (Mean±SEM) for OTFC and Morphine in AC200/010



ACTIQ™ PHARMACOKINETICS

Fentanyl Delivery Characteristics of Actiq™:

Figure 1. Plasma concentrations of fentanyl (mean±SEM) after intravenous (n=10), OTFC (n=10), or oral (n=8) administration of fentanyl 15 µg/kg.

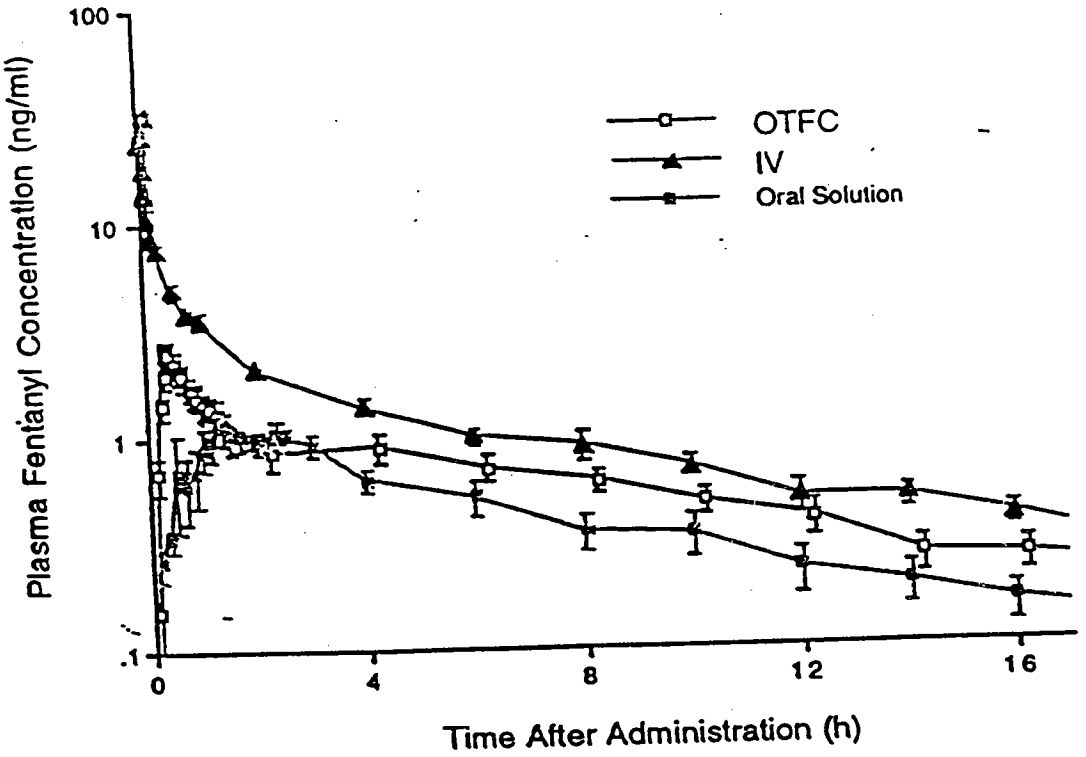


Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b])

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
Hospitalizations						
OTFC 200 µg	AC 200/014	4708	69	F	Hospitalization	Evaluation of rib pain (UNR), subdural hematoma (UNR)
OTFC 200 µg	AC 200/014	41001	53	M	Hospitalization (Withdrawal)	Uncontrolled pain and pancytopenia (UNR)
OTFC 200 µg	AC 200/014	41002	56	F	Hospitalization	Lower respiratory infection (UNR)
OTFC 200 µg	AC 200/014	41003	58	F	Hospitalization	Small bowel obstruction (UNR)
OTFC 200 µg	AC 200/014	42207	43	F	Hospitalization	Pancytopenia (UNR), fever (UNR)
OTFC 200 µg	AC 200/014	42210	72	F	Hospitalization	Pathologic fracture of the right femur (UNR)
OTFC 400 µg	AC 200/014	4110	57	F	Hospitalization (Withdrawal)	Shortness of breath (UNL)
OTFC 400 µg	AC 200/014	4115	54	F	Hospitalization	Spinal radiation therapy (UNR)
OTFC 400 µg	AC 200/014	4116	55	F	Hospitalization (Withdrawal)	Altered mental status (UNL), renal failure (UNL)
OTFC 400 µg	AC 200/014	4702	47	F	Hospitalization	Pulmonary edema (UNR)
OTFC 400 µg	AC 200/014	4703	49	F	Hospitalization	Spinal cord compression (UNR)
OTFC 400 µg	AC 200/014	42902	55	F	Hospitalization (Death)	Severe weakness (UNR)
OTFC 400 µg	AC 200/014	44301	69	F	Hospitalization (Withdrawal/Death)	Pathological left hip fracture(UNR)
OTFC 400 µg	AC 200/014	44404	65	F	Hospitalization	Pamidronate and immunoglobulin therapy because of concomitant anemia (UNR)
OTFC 400 µg	AC 200/014	44601	42	F	Hospitalization	Intractable nausea and vomiting (UNR), gastrointestinal viral infection (UNR)
OTFC 600 µg	AC 200/014	4305	55	F	Hospitalization	Nausea, vomiting, abdominal distension (UNL)
OTFC 600 µg	AC 200/014	4307	44	F	Hospitalization (Withdrawal/Death)	Bilateral lower extremity weakness (UNR), uncontrolled pain (UNR)
OTFC 600 µg	AC 200/014	42701	50	M	Hospitalization	Pancytopenia (UNR), pneumonia (UNR), nausea (UNR), vomiting (UNR), persistent headache (UNR)

Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b]) - Continued

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
OTFC 600 µg	AC 200/014	43801	68	M	Hospitalization (Withdrawal/Death)	Thrombocytopenia and anemia (UNR)
OTFC 800 µg	AC 200/014	4112	61	M	Hospitalization	Fever of unknown origin (UNR), fever and chills (UNR), sepsis (UNR)
OTFC 800 µg	AC 200/014	4202	55	F	Hospitalization (Withdrawal)	Dehydration, abdominal pain, uncontrollable pain (UNL), urinary tract infection (UNL)
OTFC 800 µg	AC 200/014	4207	52	F	Hospitalization (Withdrawal/Death)	Pneumonia and probable chronic obstructive pulmonary disease (UNR)
OTFC 800 µg	AC 200/014	4209	30	F	Hospitalization	Dehydration due to nausea and vomiting, (UNL), small bowel obstruction (UNL), pneumonia (UNR), anemia (UNR), gastrointestinal bleeding (UNR), hemoptysis (UNR)
OTFC 800 µg	AC 200/014	4308	74	M	Hospitalization	Surgical debridement of a wound (UNR)
OTFC 800 µg	AC 200/014	4311	47	F	Hospitalization (Withdrawal/Death)	Altered mental status (UNR)
OTFC 800 µg	AC 200/014	4312	59	M	Hospitalization (Withdrawal/Death)	Neutropenic sepsis (UNR), bacterial pneumonia (UNR)
OTFC 800 µg	AC 200/014	4403	55	F	Hospitalization (Withdrawal)	Chest pain, shortness of breath (UNR), uncontrollable pain (UNR)
OTFC 800 µg	AC 200/014	4706	43	M	Hospitalization (Withdrawal/Death)	Disease evaluation (UNR), disseminated intravascular coagulation (UNR), hepatorenal syndrome (UNR)
OTFC 800 µg	AC 200/014	4801	41	F	Hospitalization	Severe headaches, inability to suck and chew, disorientation (UNR)
OTFC 800 µg	AC 200/014	42206	59	F	Hospitalization (Death)	Presumed small bowel obstruction and uncontrolled abdominal pain (UNR)
OTFC 800 µg	AC 200/014	42901	45	F	Hospitalization (Withdrawal/Death)	Intramedullary of rod placement (UNR)
OTFC 800 µg	AC 200/014	43402	64	M	Hospitalization (Death)	Hemoptysis and increasing dyspnea (UNR)
OTFC 800 µg	AC 200/014	43610	74	M	Hospitalization	Uncontrollable pain (UNR)
OTFC 1200 µg	AC 200/014	4111	34	F	Hospitalization	Uncontrolled pain (UNR)
OTFC 1200 µg	AC 200/014	4114	49	F	Hospitalization (Withdrawal)	Esophageal candidiasis (UNR), dysphagia (UNR)
OTFC 1200 µg	AC 200/014	4407	68	F	Hospitalization (Withdrawal)	Reduction of hip fracture (UNR)

Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b]) - Continued

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
OTFC 1200 µg	AC 200/014	42204	69	F	Hospitalization (Death)	Fracture of right arm and rod placement in left leg (UNR)
OTFC 1200 µg	AC 200/014	42209	45	M	Hospitalization	Small bowel obstruction (UNR)
OTFC 1200 µg	AC 200/014	42504	39	F	Hospitalization	dehydration (UNR), fever (UNR), urosepsis (UNR), urinary tract infection (UNR), right ankle edema (UNR)
OTFC 1200 µg	AC 200/014	42905	56	M	Hospitalization (Death)	Deep vein thrombosis (UNR) renal insufficiency (UNL)
OTFC 1200 µg	AC 200/014	42908	58	F	Hospitalization (Withdrawal)	Loss of use of right arm (UNL), confusion (UNR)
OTFC 1200 µg	AC 200/014	43105	44	M	Hospitalization (Withdrawal)	Aspiration pneumonia (UNL), dysphagia (UNL)
OTFC 1200 µg	AC 200/014	43609	60	M	Hospitalization (Withdrawal)	Confusion (UNL), increased pain (UNL), dehydration (UNL)
OTFC 1200 µg	AC 200/014	44401	47	M	Hospitalization (Withdrawal)	Leukopenia (UNR), pneumonia (UNR)
OTFC 1200 µg	AC 200/014	44701	46	M	Hospitalization (Withdrawal)	Biliary obstruction (UNL), prolonged bleeding times (UNR)
OTFC 1200 µg	AC 200/014	44702	58	F	Hospitalization (Withdrawal)	Uncontrolled pain (UNR)
OTFC 1200 µg	AC 200/014	44703	52	F	Hospitalization (Disability)	Closed reduction of dislocated right hip (UNR)
OTFC 1600 µg	AC 200/014	4105	52	F	Hospitalization (Withdrawal)	Bacteremia (UNR)
OTFC 1600 µg	AC 200/014	4107	35	F	Hospitalization	Fever of unknown origin (UNR),dehydration and electrolyte imbalance (UNR), line urosepsis (UNR), sepsis (UNR), pyelonephritis and hydronephrosis (UNR), obstructed ureteral stent (UNR), planned surgery (UNR)
OTFC 1600 µg	AC 200/014	4108	30	F	Hospitalization	Status asthmaticus (UNR)
OTFC 1600 µg	AC 200/014	4204	59	M	Hospitalization (Withdrawal/Death)	Abdominal pain (UNL)
OTFC 1600 µg	AC 200/014	4404	68	M	Hospitalization (Withdrawal)	Severe pain (UNR), vomiting (UNR)

Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b]) - Continued

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
OTFC 1600 µg	AC 200/014	41204	67	M	Hospitalization (Withdrawal)	L-3 fracture of the lumbar spine (UNL), debridement of ulcer (UNR)
OTFC 1600 µg	AC 200/014	42202	59	F	Hospitalization (Withdrawal)	Infected biopsy site (UNR)
OTFC 1600 µg	**AC 200/014**	**42301**	**42**	**F**	**Hospitalization**	**Left hip replacement (UNR)**
OTFC 1600 µg	**AC 200/014**	**42302**	**45**	**F**	**Hospitalization**	**Hypocalcemia (UNR), sepsis (UNR), hyperglycemia (UNR), left distal radius fracture (UNR)**
OTFC 1600 µg	**AC 200/014**	**42505**	**27**	**F**	**Hospitalization**	**Fever (UNR), uncontrolled pain (UNR)**
OTFC 1600 µg	**AC 200/014**	**42606**	**69**	**M**	**Hospitalization (Withdrawal)**	**Bowel obstruction (UNL)**
OTFC 1600 µg	**AC 200/014**	**43103**	**42**	**F**	**Hospitalization**	**Uncontrolled pain (UNL)**
OTFC 1600 µg	AC 200/014	43403	52	M	Hospitalization (Death)	Severe vomiting and uncontrollable pain (UNR)
OTFC 1600 µg	**AC 200/014**	**43602**	**25**	**F**	**Hospitalization (Withdrawal)**	**Headache (UNL), Confusion (UNL), agitation (UNL), nausea (UNL), vomiting (UNL)**
OTFC 1600 µg	AC 200/014	43701	59	F	Hospitalization	Small bowel obstruction (UNR)
OTFC 1600 µg	AC 200/014	44302	48	M	Hospitalization (Death)	Fever (UNR), chills (UNR), decreased performance status (UNR), stomatitis (UNR), pancytopenia (UNR), dehydration (UNR), anemia (UNR), wasting (UNR), increased pain with swallowing (UNR), sepsis (UNR), pleural effusion (UNR)
Overdosage						
OTFC 1600 µg	AC 200/014	41206	75	M	Overdosage	Patient used 1600 µg dose rather than 200 µg for 9 days
Disability						
OTFC 1200 µg	AC 200/014	44703	52	F	Disability (Hospitalization)	Fracture of femoral head and trochanter; fracture resulted in permanent disability (UNR)

Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b]) - Continued

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
Deaths						
OTFC 200 µg	AC 200/014	4103	69	F	Death (Withdrawal)	Death due to cardiac arrest secondary to metastatic gastric cancer (UNR)
OTFC 200 µg	AC 200/014	4402	57	F	Death (Withdrawal)	Death due to disease progression (UNL)
OTFC 200 µg	AC 200/014	4704	63	M	Death (Withdrawal)	Death due to hypoxic seizure after aspirating a mucus plug (UNR)
OTFC 200 µg	AC 200/014	42502	59	F	Death (Withdrawal)	Death due to progression of ovarian cancer (UNR)
OTFC 400 µg	AC 200/014	4205	68	M	Death	Death due to disease progression (UNR)
OTFC 400 µg	AC 200/014	4701	63	F	Death (Withdrawal)	Death due to disease progression (UNR)
OTFC 400 µg	AC 200/014	4707	61	F	Death (Withdrawal)	Death due to disease progression (UNR)
OTFC 400 µg	AC 200/014	42607	54	M	Death	Death due to disease progression of lung cancer (UNR)
OTFC 400 µg	**AC 200/014**	**42902**	**55**	**F**	**Death (Hospitalization)**	**Death due to disease progression (UNR)**
OTFC 400 µg	AC 200/014	43806	48	M	Death	Death due to metastatic sarcoma (UNR)
OTFC 400 µg	**AC 200/014**	**44301**	**69**	**F**	**Death (Hospitalization/ Withdrawal)**	**Death due to disease progression (UNR)**
OTFC 600 µg	**AC 200/014**	**4307**	**44**	**F**	**Death (Hospitalization/ Withdrawal)**	**Death due to disease progression (UNR)**
OTFC 600 µg	AC 200/014	42208	48	F	Death (Withdrawal)	Death due to disease progression (UNR)
OTFC 600 µg	AC 200/014	43801	68	M	Death (Hospitalization/ Withdrawal)	Death due to disease progression (UNR)
OTFC 600 µg	AC 200/014	44202	69	M	Death	Death due to progression of metastatic rectal cancer (UNR)
OTFC 800 µg	AC 200/014	4207	52	F	Death (Hospitalization/ Withdrawal)	Death due to progressive cervical cancer (UNR)
OTFC 800 µg	AC 200/014	4311	47	F	Death (Hospitalization/ Withdrawal)	Death due to disease progression (UNR)
OTFC 800 µg	AC 200/014	4312	59	M	Death (Hospitalization/ Withdrawal)	Death due to disease progression (UNR)
OTFC 800 µg	AC 200/014	4706	43	M	Death (Hospitalization/ Withdrawal)	Death due to cardiopulmonary failure after disseminated intravascular coagulation and hepatorenal syndrome (UNR)

Table 4-14 Safety Update 1: Adverse Events - Chronic Pain Patients From an Uncontrolled Clinical Trial[a] (n = 156[b]) - Continued

Index of patients with serious adverse events (SAE) by type of SAE

Maximum Unit Dose Strength[c]	Study number	Patient ID	Age	Gender	SAE	Reason (Relationship to Study Drug[d])
OTFC 800 µg	AC 200/014	42206	59	F	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 800 µg	AC 200/014	42901	45	F	Death (Hospitalization/ Withdrawal)	Death due to progression of metastatic adenocarcinoma of the breast (UNR)
OTFC 800 µg	AC 200/014	42906	55	M	Death (Withdrawal)	Death due to disease progression (UNL)
OTFC 800 µg	AC 200/014	43402	64	M	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 1200 µg	AC 200/014	4705	59	F	Death (Withdrawal)	Death due to disease progression (UNR)
OTFC 1200 µg	AC 200/014	42204	69	F	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 1200 µg	AC 200/014	42905	56	M	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 1600 µg	AC 200/014	4101	50	M	Death	Death due to disease progression (UNR)
OTFC 1600 µg	AC 200/014	4204	59	M	Death (Hospitalization/ Withdrawal)	Death due to disease progression (UNR)
OTFC 1600 µg	AC 200/014	43403	52	M	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 1600 µg	AC 200/014	44302	48	M	Death (Hospitalization)	Death due to disease progression (UNR)
OTFC 1600 µg	AC 200/014	44303	32	F	Death	Death due to progression of metastatic adenocarcinoma of the breast (UNR)

[a]Trial: AC 200/014

[b]For serious adverse events, a later cutoff date of January 15, 1997 was used. All SAEs reported before January 15, 1997, are included in this index.

[c]Patients are indexed according to the maximum unit dose strength ever received.

[d]Relationship as reported by investigator UNR = unrelated, UNL = unlikely, POS = possibly, PRO = probably, REL = almost certainly treatment related.

4.6 Narratives - Chronic Pain Patients

There are three types of narratives that are presented in this report (update to the original ISS in NDA 20-747 submitted in November 1996). Some narratives have been revised, and some narratives include events that occurred after the original NDA submission. These narratives have introductory sentences indicating that they are revised, and the revisions are in **bold** typeface. The remainder of the narratives included in this section are new narratives and are not in bold typeface.

Patient #4107 (AC 200/014) Hospitalization

The following narrative includes events that occurred after the original NDA submission.

The patient was a 35-year-old white female with adenocarcinoma of the cervix, metastatic to the lung and liver, diagnosed in September 1993. In January 1994, the patient had a recurrence of the her cancer and underwent an anterior exteneration with Indiana pouch placement. She subsequently developed a small bowel obstruction requiring a loop jejunostomy as well as placement of a chronic indwelling right ureteral stent. The patient's medical history was significant also for chronic hypomagnesemia, hypokalemia, and metabolic acidosis. Her cancer pain was being controlled with Duragesic patch 150 µg/hour and OTFC 1200 µg by mouth as needed for breakthrough pain. The patient was also receiving GCSF for leukopenia related to her chemotherapy. The patient completed protocol AC 200/012 (#2102) and enrolled in AC200/014 on July 20, 1995, using 4 OTFC units per day. On September 26, 1995, the patient was hospitalized due to a fever of unknown origin. She was treated with intravenous antibiotics. Her symptoms resolved, and she was discharged from hospital September 30, 1995. The patient did not use OTFC on September 26 and 27, 1995. She requested that she use OTFC while in the hospital, and OTFC use was resumed on September 28, 1995. The investigator stated that the patient's hospitalization was not related to OTFC. The patient's transdermal fentanyl dose and OTFC dose had been titrated to 250 µg/hr and 1600 µg, respectively.

The patient developed increasing renal insufficiency and was scheduled for a right ureteral stent exchange and possible left stent placement on February 23, 1996. For two days prior to the patient's admission to the hospital on February 22, 1996, the patient had complained of nausea and vomiting which she attributed to "stomach flu." She was mildly dehydrated and had very low potassium (2.9 mEq/L) and low bicarbonate (11 mEq/L). She was admitted to the hospital for IV hydration and management of electrolyte abnormalities prior to her scheduled surgery. The patient continued her use of OTFC while hospitalized. She was discharged February 26, 1996. The investigator stated that this adverse event was unrelated to the use of OTFC.

The patient was readmitted to the hospital on April 4, 1996, with a 48-hour history of fever. Blood cultures from two peripheral sites and from the site of a Hickman catheter yielded Klebsiella pneumoniae and Enterococcus species. Central line urosepsis was determined to be the source of the infection. She was treated with IV Ceftazadime 1 gm every 12 hours and vancomycin 500 mg IV every 12 hours. She was discharged home on April 7, 1996, on ampicillin 200 mg PO four times daily and Keflex 250 mg PO four times daily for seven days. The patient continued the use of OTFC during this time. The investigator has stated that this adverse event was unrelated to the use of OTFC.

The patient had a low hemoglobin level (7.5 g/dL) during her hospitalization and presented to the clinic on April 10, 1996, for an outpatient transfusion of one unit of packed red blood cells. She was noted to have chills and a temperature of 101.5° F. She was admitted to the hospital

the same day for presumed central line sepsis. Her Hickman catheter was removed, and she was treated with ampicillin 1 gm IV every six hours and with Ceftazadime 1 gm IV every twelve hours. The patient was discharged home on April 12, 1996, with her IV antibiotics continuing. The patient continued with her pain medications unchanged during this hospitalization. The investigator has stated that this adverse event was unrelated to the use of OTFC.

The patient was admitted to the hospital again on April 25, 1996. She presented with flank pain and a fever which had been ongoing for the previous several days. Urine cultures grew Candida albicans, and a renal ultrasound was done. She was diagnosed with pyelonephritis and hydronephrosis. The patient was treated with Fortaz 1 gram IV every 12 hours, ampicillin 1 gram IV every 6 hours , and fluconazole 100 mg every 12 hours. Her cancer pain medications, including OTFC, were continued while she was hospitalized, but in addition, she was given IV morphine, 1-6 mg IV, for her flank pain. Her stent was removed on May 3, and she was discharged from the hospital on May 6, 1996. The investigator has stated that this adverse event was unrelated to the use of OTFC.

On August 29, 1996, the patient developed a urinary tract infection rated as moderate. She presented to the hospital on August 30, 1996, with obstructed ureteral stents. The stents were removed, and a percutaneous nephrostomy was placed. The patient was placed on intravenous antibiotics. Use of OTFC 1600 µg continued while she was hospitalized. The patient was discharged on September 2, 1996. The investigator determined this event was unrelated to the use of OTFC.

On November 12, 1996, the patient was admitted to the hospital for planned surgical repair of her Indiana pouch, a right nephrostomy, elevation of her ileostomy with a possible anastomosis and possible colostomy. Her transdermanl fentanyl had been titrated to 300 µg/hr for around-the-clock pain, and she was using OTFC 1600 µg as needed for breakthrough pain. Use of OTFC 1600 µg was discontinued while she was hospitalized, with the last dose taken November 12, 1996, prior to hospitalization. Use of OTFC resumed when the patient was discharged on November 26, 1996. The investigator stated this event was unrelated to the use of OTFC.

Patient #4114 (AC 200/014) Withdrawal/Hospitalization
The following narrative has been revised from the ISS submission.

Patient #4114 was a 49 year old Hispanic female with metastatic breast cancer diagnosed in October 1991. The patient completed protocol AC 200/011 (#1116) and was enrolled in protocol AC 200/014 on May 16, 1996. She was using MS Contin 180 mg every 12 hours for control of her around the clock pain, mexiletine and Elavil to control her neuropathic pain, and MSIR as needed for breakthrough pain. The patient had not taken any OTFC since July 17, 1996, when she was placed on hold so she could participate in an Allovectin-7 protocol.

On July 27, 1996, the patient reported having difficulty swallowing. On July 29, 1996, the patient was admitted to the hospital with a diagnosis of esophageal candidiasis. The Allovectin-7 was discontinued, and the patient was treated with fluconazole. **On July 30, 1996, the decision was made to withdraw the patient from the study due to her dysphagia, and she was placed on a continuous sub-cutaneous morphine pump. The last dose of OTFC was consumed on that day.** The patient was

discharged home on August 3, 1996. The investigator stated that this event was unrelated to use of study drug.

Patient #4116 (AC 200/014) Withdrawal/Hospitalization

Patient #4116 was a 55-year-old white female, weighing 97.8 pounds, with metastatic rectal cancer diagnosed in January 1993. She completed protocol AC 200/012 (#2107) and entered protocol AC 200/014 on July 10, 1996. She was using transdermal fentanyl 50 µg/hr for around-the-clock pain, Elavil 25 mg nightly for neuropathic pain, and OTFC 200 µg or Vicodin 1-2 tablets as needed for breakthrough pain. The patient's right kidney was completely dysfunctional, and her left kidney had a large nephrostomy. She had a recent history of renal azotemia. On September 24, 1996, the patient's creatinine was 3.5 mg/dL.

The patient presented to the after hours clinic on September 29, 1996, complaining of "not feeling quite right", and was admitted to the hospital that day for altered mental status and renal failure. Altered mental status was rated as severe, and renal failure was severe. The patient had stents and nephrostomy tubing placed on October 4, 1996. On October 9, 1995, her creatinine was 2.1 mg/dL, and her mental status remained altered. The last dose of OTFC was taken on October 5, 1996. The patient was discontinued from the study on October 9, 1996. The patient was discharged on October 11, 1996. The investigator has stated this event was unlikely related to the use of OTFC.

Patient #4209 (AC 200/014) Hospitalization

The following narrative includes events that occurred after the original NDA submission.

Patient #4209 was a 31-year-old white female, weighing 88 pounds, with metastatic ovarian cancer diagnosed in December 1994. The patient successfully completed protocol AC 200/011 (#1209) and was enrolled in extension protocol AC 200/014 on April 10, 1996. She was using MS Contin 30 mg twice daily for around-the-clock control of her cancer pain. MSIR 10-20 mg and OTFC 800 µg were used as needed for treatment of breakthrough pain. The patient also had a history of chronic diarrhea for which she was taking Lomotil.

On May 10, 1996, the patient was admitted to the hospital for dehydration secondary to nausea and vomiting which she and her physician believed were most likely related to her chemotherapy. The patient was rehydrated with IV fluids and she received Zofran, 8 mg IV every 8 hours as needed for nausea and vomiting. Her hemoglobin was 7.7 g/dL, and her hematocrit was 22.7% on May 12, 1996, so she also received two units of packed red blood cells for anemia and poor nutrition. The patient continued to use OTFC and her regular pain medications while hospitalized. She was discharged from the hospital on May 13, 1996. The investigator indicated that these adverse events and subsequent hospitalization were unlikely to be related to the use of OTFC.

On May 30, 1996, the patient was admitted to the hospital with nausea, vomiting, and fever. She also had hyponatremia and hypokalemia with alkalosis. The patient was treated with IV fluids and potassium chloride. Abdominal radiograms revealed a small bowel obstruction, and a decompression gastrostomy was performed on June 4, 1996. The patient continued to use OTFC and her regular pain medications while hospitalized. She was discharged from the hospital on June 6, 1996. The investigator indicated that these adverse events and subsequent hospitalization were unlikely to be related to the use of OTFC.

On July 19, 1996, she presented to the clinic with a cough and a 102° fever. The patient was diagnosed with pneumonia and admitted to the hospital this same day. The patient continued using OTFC to treat her breakthrough pain while in the hospital. She was released on July 22,

1996. The investigator stated that the patient's pneumonia and subsequent hospitalization were unrelated to OTFC.

On December 9, 1996, the patient fainted and was taken to the emergency room. Her complete blood count revealed a decreased hematocrit, and she was admitted to the hospital on that day with a diagnosis of anemia and gastrointestinal bleeding which were considered to be unrelated to OTFC. She was given 2 units of packed red blood cells and placed on total parenteral nutrition. The patient's MS Contin had been titrated to 130 mg twice a day. Use of OTFC 800 µg and regular pain medications continued while she was hospitalized. The patient was discharged on December 12, 1996.

On December 22, 1996, the patient was admitted to the hospital for nausea and vomiting. She was given three units of packed red blood cells for anemia. Use of OTFC 800 µg continued during hospitalization. The nausea and vomiting resolved, and she was discharged on December 24, 1996. The investigator determined this event was unrelated to the use of OTFC.

The patient was again hospitalized on December 30, 1996, for nausea and vomiting. She was again given three units of packed red blood cells for anemia. Use of OTFC 800 µg continued while she was hospitalized. The nausea and vomiting resolved, and she was discharged on January 1, 1997. The investigator indicated these events were unrelated to the use of OTFC.

On January 13, 1997, the patient was admitted to the hospital with severe hemoptysis, which had begun the previous day. Laboratory results showed she had a decreased hemoglobin and was hypokalemic. The patient was given two units of packed red blood cells and intravenous potassium chloride 60 mg. Use of OTFC 800 µg continued while she was hospitalized. She remains hospitalized at the time of the writing of this narrative. The investigator determined this event was unrelated to the use of OTFC.

Patient #4307 (AC 200/014) Withdrawal/Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #4307 was a 44-year-old asian female with metastatic ovarian cancer diagnosed in January 1995. The patient completed protocol AC 200/012 (#2304) and was enrolled in protocol AC 200/014 on January 19, 1996. During the course of the study, the patient was titrated to methadone 160 mg four times a day and Decadron 40 mg a day for around-the-clock pain, and OTFC 600 mcg as needed for treatment of breakthrough pain. She was also using Coumadin at varied doses for deep vein thrombosis. She was admitted to the hospital on August 19, 1996, with progressive bilateral lower extremity weakness over the previous three days. Spinal cord compression was ruled out. The patient was discharged home on August 24, 1996. The last dose of OTFC prior to hospital admission was taken on August 16, 1996. Despite OTFC being available to her, the patient did not take the next OTFC dose until August 20, 1996. The investigator indicated that this adverse event was unrelated to the use of OTFC.

The patient was experiencing increased pain and was admitted to the hospital on September 18, 1996, to stabilize her pain. She was treated with intravenous Decadron and methadone for her around-the-clock pain and intravenous antibiotics for bacteremia. The patient continued to use OTFC.

while hospitalized, taking her last dose on September 24, 1996. She was withdrawn from the study on September 25, 1996, because of plans to discharge her to a nursing care facility due to her disease progression. The patient died as a result of cardiopulmonary arrest on September 27, 1996, without being discharged. The investigator indicated that this adverse event was unrelated to the use of OTFC.

Patient #4312 (AC 200/014) Withdrawal/Hospitalization/Death
The following narrative contains information on this patient from two studies, AC 200/012 and AC 200/014 and has been revised from the ISS submission.

Patient #2307 was a 59 year-old male undergoing chemotherapy for lung cancer metastatic to spine and chest wall. He was using Duragesic, 175 µg/hr, for around-the-clock control of his cancer pain, and oxycodone, 5 mg as needed, for treatment of breakthrough pain. He was enrolled in protocol AC 200/012 and took his first dose of OTFC, 400 µg, on June 13, 1996.

On June 20, 1996, the patient complained of chills and malaise and was admitted to the hospital for presumed neutropenic sepsis related to chemotherapy administered on June 14, 1996. He was treated with Timentin and gentamicin, and was discharged from the hospital on June 25, 1996. His last dose of OTFC, 600 µg, prior to his hospitalization was taken on June 18, 1996, and treatment was temporarily suspended while the patient was hospitalized. The patient resumed taking OTFC after discharge and successfully completed the study on 800 µg OTFC. The investigator stated that this adverse event was unrelated to the use of OTFC.

Patient #4312 was using Duragesic 175 µg per hour and **amitriptyline 25 mg every night for around-the-clock control of his cancer pain. Additionally he was using oxycodone 5 mg as needed or OTFC 800 µg as needed for treatment of breakthrough pain.** He completed protocol AC 200/012 (#2307) and was enrolled in protocol AC 200/014 on July 16, 1996. On June 20, 1996, while in protocol AC 200/012, the patient was admitted to the hospital for neutropenic sepsis related to chemotherapy.

On August 6, 1996, the patient was again admitted to the hospital for neutropenic sepsis due to chemotherapy administered on August 2, 1996. He was treated with Timentin and gentamicin. The patient continued the use of OTFC while hospitalized. He was discharged on August 10, 1996. The investigator has indicated that these adverse events were unrelated to OTFC.

On August 18, 1996, the patient was admitted to the hospital with a diagnosis of bacterial pneumonia. The patient was treated with Bactrim, ceftazidime, clindamycin, Proventil, and oxygen. **The decision was made to withdraw the patient from the study at this point as his condition was deteriorating.** His last dose of OTFC was taken on August 17, 1996. The patient's condition became progressively worse, and he died on August 30, 1996, without being discharged. The investigator has indicated that these adverse events were unrelated to the use of OTFC

Patient #4404 (AC 200/014) Withdrawal/Hospitalization
Patient #4404 was a 68-year-old white male with liver cancer diagnosed in April 28, 1995, and retroperitoneal adenopathy diagnosed in May 1995. He completed protocol AC 200/011 (#1403) and entered protocol AC 200/014 on August 4, 1995. He was using MS Contin 390 mg daily for around-the-clock pain, and OTFC 1600 µg as needed for breakthrough pain.

The patient experienced severe, sudden onset of pain and vomiting on August 26, 1996, and was admitted to the hospital that day to rule out an intestinal obstruction. All current pain

medications were stopped at that time, with the last dose of OTFC taken earlier the day of admission. While in the hospital, the patient was placed on oral Dilaudid every two hours until a dose was reached that made him comfortable. No obstruction was found and when discharged on August 30, 1996, he was using Dilaudid 36 mg every 2 hours for his around-the-clock pain. Use of OTFC resumed on September 3, 1996. The investigator has determined these events are unrelated to the use of OTFC.

The patient withdrew from the study on September 10, 1996, due to increasing urinary frequency and general disease progression which were considered unrelated to OTFC. The last OTFC dose was consumed on that day.

Patient #4703 (AC 200/014) Hospitalization

Patient #4703 was a 49-year-old white female with metastatic breast cancer diagnosed in 1990. She successfully completed protocol AC 200/011 (#1702) and was enrolled in protocol AC 200/014 on August 6, 1995. The patient was using MS Contin 45 mg every eight hours for around-the-clock pain. MSIR 30 mg or OTFC 600 µg was used as needed for treatment of breakthrough pain.

During a routine office visit on October 17, 1996, it was noticed that the patient was hyperreflexic in the lower extremities. She was placed on dexamethasone 4 mg twice a day for possible spinal cord compression. On November 4, 1996, the patient noticed some spasticity of her lower extremities which worsened over the next 72 hours. On November 7, 1996, she had difficulty supporting her weight, and was admitted to the hospital on that date for impending spinal cord compression of moderate severity. A computerized tomography (CT) scan of the abdomen and T8 vertebral body was done. There were no significant findings on the abdominal scan and no evidence of hepatic metastatic disease or ascites. The T8 and T9 vertebral bodies showed extensive damage. This area had received extensive irradiation previously. Because of the limitations of CT scans in assessing spinal cord compression, she was scheduled for a magnetic resonance imaging (MRI) study. The patient began intravenous dexamethasone 10 mg. While hospitalized, the T8 and T9 vertebral bodies were removed, and she was stabilized between the T7 and T10 vertebral bodies. Use of OTFC 600 µg continued during the hospitalization. The patient was discharged on November 21, 1996. The investigator indicated this event was unrelated to the use of OTFC.

Patient #4708 (AC 200/014) Hospitalization

The following narrative has been revised from the ISS included in the original NDA submission.

Patient #4708 was a 69-year-old white female with breast cancer metastatic to bone and brain diagnosed in January 1991. She successfully completed protocol AC 200/012 (#2702) and was enrolled in extension protocol AC 200/014 on May 24, 1996. The patient was using Duragesic 75 µg/hr for around-the-clock control of her cancer pain. MSIR 15 mg or OTFC 200 µg was used as needed for treatment of breakthrough pain. The patient was also on Coumadin for a "hyercoagulable state" and a history of deep venous and superficial vein thrombophlebitis.

The patient used a walker to assist with ambulation and at 0400 on July 4, 1996, while attempting to go to the bathroom, fell as a result of using her walker improperly. The fall resulted in left back pain for which she was admitted to the hospital for evaluation. Radiograms of her ribs and multiple sites of known pathology did not reveal any fractures. The patient was discharged to an extended care facility for rehabilitation on July 6, 1996, at her

family's request. The patient continued to use OTFC during this interval. The investigator has indicated that this adverse event was unrelated to the use of OTFC.

On August 21, 1996, the patient presented to the emergency room with a 3 day history of increasing weakness, lethargy, worsening headaches associated with nausea and vomiting, and decreased appetite. She was admitted to the hospital on that day. A computerized tomography scan and magnetic resonance imaging scan were positive for a subdural accumulation in the posterior fossa which appeared to be blood. A mixture of tumor and blood could not be excluded. On admission, the patient's platelet count was 25,000, protime was 31.1 seconds, and partial thromboplastin time was greater than 200 seconds. A craniotomy with evacuation of a hematoma was performed. She was placed on intravenous Decadron 8 mg every 4 hours and was given platelets to maintain her platelet count. Her Coumadin had been discontinued on the day of admission, as was OTFC. Use of OTFC was resumed on August 29, 1996. The patient was discharged on September 5, 1996. The investigator has indicated that this adverse event was unrelated to the use of OTFC.

Patient #42201 (AC 200/014) Withdrawal
Patient #42201 was a 65-year-old white male with multiple myeloma diagnosed in April of 1993. He completed protocol AC 200/013 (#32201) and entered protocol AC 200/014 on January 12, 1996. He was using MS Contin 120 mg twice a day for around-the-clock pain, and Tylox 2 tabs as needed or OTFC 1600 µg as needed for breakthrough pain. During the course of the study, he was titrated down to OTFC 1200 µg. On October, 24 1996, the patient withdrew his consent for the study due to increased pain, and was switched to a morphine pump. The last dose of OTFC was consumed on that same day. The investigator considered this adverse event unrelated to OTFC.

Patient #42204 (AC 200/014) Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #42204 was a 69-year-old white female diagnosed with breast cancer in August 1991. The patient completed protocol AC 200/013 (#32206) and was enrolled in extension protocol AC 200/014 on April 24, 1996. The patient was using MS Contin 60 mg twice a day and Naprosyn 500 mg every 8 hours for around-the-clock pain, and OTFC 1200 mcg as needed or Roxicet 1 tablet as needed was used for breakthrough pain. On August 9, 1996, the patient was admitted to the hospital for a fractured right arm, resulting from a fall, and to prophylactically have a rod placed in her left leg. The patient continued to use her OTFC while in the hospital. The investigator considered these adverse events unrelated to OTFC.

The patient took her last dose of OTFC on September 13, 1996, and was admitted to in-patient hospice care on September 15, 1996. She died on September 17, 1996, as a result of her disease progression. The investigator has determined that this adverse event was unrelated to the use of OTFC.

Patient #42206 (AC 200/014) Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #42206 is a 59 year-old white female with ovarian cancer diagnosed in December 1991. Her medical history is significant also for obesity, diabetes, hypertension, arthritis, gout, depression, constipation, and small bowel obstruction on several occasions. The patient successfully completed protocol AC 200/013 (#32209) and was enrolled in extension protocol AC 200/014 on April 30, 1996. She was taking Oramorph 60 mg daily for around-the-clock

control of her cancer pain, and OTFC 600 µg as needed (approximately twice daily) for treatment of breakthrough pain. On May 20, 1996, she began to experience nausea and vomiting and on the following day this was accompanied by increased abdominal pain. She was admitted to the hospital on May 21, 1996, for a presumed small bowel obstruction and uncontrolled abdominal pain. A radiograph could not confirm or rule out an obstruction. She was treated with IV fluids and a nasogastric tube was placed. She was discharged on May 26, 1996. The patient continued the use of OTFC while she was hospitalized. The investigator indicated that these adverse events leading to hospitalization were unrelated to the use of OTFC.

The patient died at home on October 25, 1996, as a result of her disease progression. The last dose of OTFC 800 µg was taken on October 22, 1996. The investigator indicated this event was unrelated to the use of OTFC.

Patient #42207 (AC 200/014) Hospitalization

The following narrative contains information on this patient from two studies, AC 200/013 and AC 200/014.

Patient #32205 was a 43-year-old white female with breast cancer metastatic to bone, lung, and liver. Her cancer pain was controlled with MS Contin, 60 mg twice daily, and Percocet, two tabs, as needed. The patient was enrolled in protocol AC 200/013 on April 1, 1996. She received satisfactory pain control with 200 µg units of OTFC and she entered phase 2, taking her first dose on April 9, 1996. She complained of a severe headache and mild shortness of breath prior to taking the first dose of study medication on that date. The following day she presented at the clinic with moderate lethargy, weakness, pallor, and a temperature of 102.4° F. She also complained of left flank pain, and appeared to be over-sedated.

She was admitted to the hospital on April 10, 1996, with possible urosepsis. Blood and urine specimens were taken for culture, but were negative. She was diagnosed with severe pneumonia which was confirmed on a chest radiogram and she was severely dehydrated. The patient was treated with IV fluids and with Timentin, 3.1 g IV, every six hours. MS Contin was lowered to 30 mg every 12 hours because of suspected over-sedation, and her OTFC was discontinued while she was hospitalized. The patient was discharged from the hospital on April 22, 1996. She resumed the use of OTFC on April 25, and successfully completed the study. The investigator states that these adverse events are unlikely to be related to the use of OTFC.

Patient #42207 was a 43-year-old white female with breast cancer metastatic to bone, lung, and liver diagnosed in October 1978. She successfully completed protocol AC200/013 (#32205) and was enrolled in protocol AC200/014 on May 7, 1996. The patient was using MS Contin 60 mg twice a day for around-the-clock pain. OTFC 200 µg or Percocet 2 tabs were used as needed for treatment of breakthrough pain. The patient was hospitalized April 10, 1996, through April 22, 1996, for pneumonia and dehydration.

On June 11, 1996, the patient was admitted to the hospital with fever which had started the previous day, granulocytopenia, and pancytopenia following chemotherapy. The patient was treated with acetaminophen, Ciprofloxacin, vancomycin, Fortaz, and Neupogen. The patient's fever resolved, and the patient was discharged on June 16, 1996. OTFC use continued during the patient's hospitalization. The investigator has determined that these adverse events were unrelated to the use of OTFC.

Patient #42209 (AC 200/014) Hospitalization
Patient #42209 was a 45-year-old white male with mucinous adenocarcinoma diagnosed October 24, 1995. He successfully completed protocol AC200/013 (#32214) and was enrolled in protocol AC200/014 on May 30, 1996. The patient was using MS Contin, 60 mg every eight hours, for around-the-clock pain. OTFC, 1200 µg, was used as needed for treatment of breakthrough pain.

On October 18, 1996, the patient was admitted to the hospital with nausea and vomiting, diarrhea, and dehydration. Physical examination suggested a small bowel obstruction, which was confirmed by radiographic studies. The patient was treated with nasogastric suction and intravenous fluids. All symptoms resolved, and the patient was discharged on October 21, 1996. OTFC use continued during the patient's hospitalization. The investigator determined that these adverse events were unrelated to the use of OTFC. It was noted that the patient had received chemotherapy prior to this hospitalization which may have contributed to his symptoms.

Patient #42211 (AC 200/014) Withdrawal
Patient #42211 was a 78-year-old white female with small cell lung cancer diagnosed on July 7, 1995. She completed protocol AC 200/013 (#32216) and entered protocol AC 200/014 on July 16, 1996. She was using MS Contin 30 mg twice a day for control of her around-the-clock pain and Percocet 2 tabs as needed or OTFC 400 µg as needed for breakthrough pain. During the course of the study, the patient was changed to MS Contin 230 mg daily for around-the-clock pain. On November 1, 1996, the patient reported developing mouth sores rated by the investigator as almost certainly related to OTFC. On that day, the patient withdrew her consent due to her mouth sores and the increasing burden of filling out the study diaries. The last dose of OTFC was consumed on October 31, 1996.

Patient #42301 (AC 200/014) Hospitalization
Patient #42301 was a 42-year-old white female with bladder cancer diagnosed in December 1980 and breast cancer metastatic to bone diagnosed in March 1989. The patient successfully completed protocol AC 200/013 (#32301) and was enrolled in protocol AC 200/014 on January 24, 1996. She was using MS Contin 600 mg four times a daily for around-the-clock pain and OTFC 1600 µg as needed for breakthrough pain.

On January 10, 1997, the patient was admitted to the hospital for a left hip replacement, following increasing pain of several weeks duration. Use of OTFC 1600 µg continued while she was hospitalized. The patient was discharged on January 16, 1997. The investigator indicated this adverse event was unrelated to the use of OTFC.

Patient #42302 (AC 200/014) Hospitalization
Patient #42302 was a 45-year-old white female with metastatic breast cancer diagnosed in October 1990. The patient successfully completed protocol AC 200/013 (#32302) and was enrolled in protocol AC 200/014 on February 10, 1996. She was using Roxanol 40 mg every four hours and aspirin two tablets every four hours for around-the-clock pain. OTFC 800 µg as needed was used for breakthrough pain.

On July 8, 1996, the patient had a serum calcium of 3.7 mEq/L, and was hospitalized for moderate hypocalcemia. She was treated with intravenous fluids and calcium. Her serum calcium improved to 10.8 mg/dL on July 9, 1996. Use of OTFC 1200 µg continued while she was hospitalized. She was discharged on July 11, 1996. The investigator indicated this adverse event was unrelated to the use of OTFC.

On September 4, 1996, the patient had a fever of 103° F and shaking chills following a port-a-cath flush. She was admitted to the hospital that day for moderate sepsis and mild hyperglycemia. Blood cultures were positive for Enterobacter cloacae. She was treated with intravenous vancomycin, ofloxacin, and insulin. She was using Decadron 4 mg three times a day for her brain metastases. Use of OTFC 1600 µg continued while she was hospitalized. The patient was discharged on September 13, 1996, on intravenous Ofloxacilin 400 mg every 12 hours and Micronase 280 mg twice a day. The investigator indicated these events were unrelated to the use of OTFC.

On October 13, 1996, the patient was hospitalized for a fractured left distal radius. She was using MS Contin 60 mg four times a day for around-the-clock pain. Roxanol 60 mg three times a day, or Darvocet 1 tablet as needed or OTFC 1600 µg as needed was used for breakthrough pain. Use of OTFC 1600 µg continued while she was hospitalized. The arm was immobilized, and she was discharged on October 14, 1996. The investigator indicated these events were unrelated to the use of OTFC.

On November 13, 1996, the patient was hospitalized for mild sepsis. Blood cultures were positive for Enterobacter and possible coagulase negative Staphylococcus. She was treated with intravenous ofloxacin, vancomycin, gentamicin, and ceftazidime. Use of OTFC 1600 µg continued while she was hospitalized. The patient was discharged on December 3, 1996. The investigator indicated this event was unrelated to the use of OTFC.

Patient # 42504 (AC 200/014) Hospitalization

Patient # 42504 was a 39-year-old white female with cervical cancer diagnosed in 1981. The patient successfully completed protocol AC 200/013 (#32507) and entered protocol AC 200/014 on June 24, 1996. She was using Duragesic 50 µg/hr, for around-the-clock pain, and Vicodin 1 tablet as needed, or OTFC 800 µg as needed for breakthrough pain.

On July 23, 1996, the patient was hospitalized for severe dehydration and a mild fever. She was given intravenous fluids, and the events resolved. She had titrated to Duragesic 200 µg/hr for around-the-clock pain, and OTFC 1200 µg as needed for breakthrough pain. The last dose of OTFC prior to hospitalization was July 21, 1996, and further use of OTFC was discontinued until discharge on July 27, 1996. The investigator indicated these events were unrelated to the use of OTFC.

On August 16, 1996, the patient was hospitalized for severe urosepsis which had begun on August 14, 1996. She was treated with intravenous fluids, intravenous Floxin 400 mg every 12 hours, intravenous Compazine 3 mg, and Tylenol 2 tablets. The last dose of OTFC 1200 µg prior to hospitalization was on August 14, 1996, and further use was discontinued until discharged on August 20, 1996. The investigator indicated these events were unrelated to the use of OTFC.

On September 12, 1996, the patient was hospitalized for severe dehydration, a moderately severe urinary tract infection, and moderate right ankle edema. She was using Duragesic 150 µg/hr for around-the-clock pain. The patient was treated with intravenous fluids and potassium, Cipro 500 mg nightly and given Jobst stockings. The last dose of OTFC 1200 µg prior to admission was taken on September 11, 1996, and use was discontinued while she was hospitalized. The patient was discharged on September 16, 1996. Use of OTFC resumed following discharge. The investigator indicated these events were unrelated to the use of OTFC.

Patient # 42505 (AC 200/014) Hospitalization
Patient # 42505 was a 27-year-old white female with cervical cancer diagnosed in November 1995. The patient successfully completed protocol AC 200/013 (#32509) and entered protocol AC 200/014 on July 23, 1996. She was using Duragesic 100 µg/hr for around-the-clock pain, and MSIR 30 mg as needed or OTFC 1200 µg as needed for breakthrough pain.

On September 1, 1996, the patient began to experience a moderate fever, and on September 6, 1996, she experienced severe uncontrolled pain. The patient was admitted to the hospital on September 6, 1996. She was treated with intravenous morphine, and Diflucan. The last dose of OTFC 1600 µg prior to hospitalization was September 6, 1996, and further use was discontinued while she was hospitalized. Her fever resolved and pain control improved on intravenous morphine. She was using MS Contin, 60 mg three times a day, for around-the-clock pain when discharged on September 12, 1996. Use of OTFC resumed after discharge. The investigator indicated these events were unrelated to the use of OTFC.

Patient #42603 (AC 200/014) Withdrawal
Patient #42603 was a 46-year-old white male with lung cancer diagnosed in February 1995. He completed protocol AC 200/013 (#32606) and entered protocol AC 200/014 on May 20, 1996. The patient was using Oramorph 30 mg three times a day for around-the-clock pain and Roxilox 1 tab as needed or OTFC 1200 µg as needed for breakthrough pain. On May 21, 1996, he began experiencing nausea and vomiting rated by the investigator as possibly related to OTFC. OTFC was suspendeduntil June 6, 1996. On June 8, 1996, the patient withdrew from the study as his nausea and vomiting did not resolve. The last dose of OTFC was consumed on that day.

Patient #42606 (AC 200/014) Withdrawal/Hospitalization
Patient #42606 was a 69-year-old white male diagnosed with colon cancer in 1993. The patient completed protocol AC 200/013 (#32609) and was enrolled in protocol AC 200/014 on July 2, 1996. At the time of enrollment, he was using transdermal fentanyl 75 µg/hr for around-the-clock pain and OTFC 800 µg as needed for breakthrough pain. While participating in the study, his transdermal fentanyl was increased to 150 µg/hr for around-the-clock pain. On October 3, 1996, his OTFC was titrated to 1600 µg as needed for breakthrough pain.

On October 13, 1996, the patient was admitted to the hospital with a severe bowel obstruction secondary to tumor growth. No intervention was done to correct the obstruction. The patient continued to use OTFC while hospitalized until his last dose on October 15, 1996, when he was discontinued from the study due to increased pain. He was discharged home on November 4, 1996. The investigator indicated that this event was unlikely related to the use of OTFC.

Patient #42607 (AC 200/014) Death
The following narrative has been revised from the ISS included in the original NDA submission.

Patient #42607 was a 54-year-old white male with lung cancer diagnosed in April 1993. The patient completed protocol AC 200/013 (#32611) and enrolled in protocol AC 200/014 on July 3, 1996. On July 17, 1996, the patient began radiation therapy for treatment of left upper lobe atelectasis. The patient died at 2110 on August 28, 1996, from progression of his lung cancer. At the time of death, he was using Morphine elixer 7.5 mg every four hours for around-the-clock control of his cancer pain. OTFC 400 µg as needed was used for treatment of breakthrough pain. The last dose of OTFC was taken at 2100 on August 27, 1996. The investigator has indicated that this event was unrelated to the use of OTFC.

Patient #42701 (AC 200/014) Hospitalization
The following narrative contains information on this patient from two studies, AC 200/013 and AC 200/014.

Patient #32701 was a 50-year-old white male with metastatic multiple myeloma undergoing chemotherapy. Anemia and neutropenia were frequent sequelae of his chemotherapy for which he received Procrit and GM-CSF. The patient was taking MS Contin, 150 mg per day, for around-the-clock control of his cancer pain and Percocet, 1 tab, as needed for treatment of breakthrough pain. He was enrolled in protocol AC 200/013 and received his first dose of OTFC on June 2, 1996. He was titrated up to an effective dose of 400 µg OTFC.

On June 4, 1996, the patient presented to the emergency room with fever and chills associated with pancytopenia and was admitted to the hospital. The patient had had chemotherapy administrations one week prior to his hospitalization and most recently on the day of admission. He was started on ceftazidime, 1 gm IV, and gentamicin, 100 mg IV, every eight hours. Blood and urine cultures, and a chest radiogram were all negative. The patient was given Procrit, 10,000 units, and GM-CSF, 500 µg, daily. He also received 2 units of packed red blood cells and 6 units of platelets. The patient continued to use OTFC while hospitalized. He was discharged from the hospital on June 6, 1996, and entered phase 2 of the study. The investigator has determined that this adverse event was unrelated to the use of OTFC.

Patient #42701 was a 50-year-old white male with metastatic multiple myeloma diagnosed in April 1991. He was undergoing chemotherapy. Anemia and neutropenia were frequent sequelae of his chemotherapy for which he received Procrit and GMCSF. The patient was taking MS Contin 150 mg per day for around-the-clock pain, and Percocet 1 tab as needed or OTFC 400 µg as needed for of breakthrough pain. He completed protocol AC 200/013 (#32701) and enrolled in protocol AC 200/014 on June 27, 1996.

On December 16, 1996, the patient complained of moderate fever, moderate cough, and severe left posterolateral chest pain. He was admitted to the hospital on December 17, 1996, with a diagnosis of pneumonia. The last dose of OTFC while hospitalized was taken on December 18, 1996, and further use was suspended until he was discharged. He was treated with Procrit 20,000 units daily for five days, GMCSF 500 µg and intravenous erythromycin and ceftizoxime. When discharged on December 20, 1996, the patient was using Biaxin 500 mg twice a day. The investigator determined these events were unrelated to the use of OTFC.

On December 25, 1996, the patient was admitted to the hospital for severe nausea and vomiting, and persistent headaches. The last dose of OTFC 400 µg was December 23, 1996, and further use was discontinued until he was discharged. During hospitalization he was treated with Bactrim DS 1 tablet twice a day, Procrit 20,000 units daily for five days, GMCSF 500 µg, and Tylenol 650 mg as needed for headache. Use of Biaxin was discontinued, and the nausea and vomiting improved. The patient was scheduled for a magnetic resonance imaging (MRI) on December 27, 1996, to determine the cause of the persistent headaches. He was discharged on December 27, 1996. The investigator determined these events were unrelated to the use of OTFC.

Patient. #42902 (AC 200/013) Hospitalization/Death
The following narrative contains information on this patient from two studies, AC 200/013 and AC 200/014.

Patient #32902 was a 55-year-old white female with stage IIIB adenocarcinoma of the lung with invasion into the vertebral bodies. Her medical history was also significant for

esophagitis for which she took Zantac, 150 mg PO twice daily, and constipation, which was treated with Colace and Senokot. She was enrolled in protocol AC 200/013 on February 16, 1996. The patient was using MS Contin, 30 mg twice daily, for around-the-clock control of her cancer pain; Tylox, 1-2 tablets; and OTFC, 400 µg, as needed for treatment of breakthrough pain.

On February 19, 1996, the patient experienced an episode of lightheadedness for 30 minutes while shopping. Approximately six hours elapsed between the time of her last dose of OTFC (400 µg) and the episode of lightheadedness. She was seen at a local emergency room in her home town, but was found only to be markedly constipated. She was then transported by her daughter to Research Medical Center in Kansas City, Missouri, where she was admitted at her request for evaluation of recurrent gastrointestinal problems. The patient was found to have a partial esophageal obstruction secondary to her adenocarcinoma and gastroesophageal reflux with attendant pain. Laboratory values were in line with a mildly dehydrated patient. The patient was hydrated and, while hospitalized, received scheduled radiation therapy. The patient continued to use MS Contin, Tylox, and OTFC for pain relief and no further episodes of lightheadedness were reported. She was discharged from the hospital on February 24, 1996. The investigator stated that he did not believe that the patient's adverse events were related to the use of the study drug. The patient resumed OTFC use and successfully completed the double-blind phase of the study.

Patient #42902 was a 55-year-old female with stage IIIb adenocarcinoma of the lung with invasion into the vertebral bodies diagnosed February 01, 1996. Her medical history was also significant for esophagitis for which she took Zantac 150 mg PO twice daily. She successfully completed protocol AC 200/013 (#32902) and was enrolled in protocol AC 200/014 on March 1, 1996. The patient was using MS Contin 60 mg twice daily for around-the-clock control of her cancer pain, and Tylox 1-2 tablets or OTFC 400 mcg as needed for breakthrough pain.

On December 31, 1996, the patient was admitted to the hospital for severe weakness. The last dose of OTFC 400 µg was December 30, 1996, and further use was withheld. Because the patient also had an esophageal obstruction, she was placed on total parenteral nutrition. She was started on patient controlled analgesia with intravenous morphine 1 mg every 10 minutes as needed for pain. The patient died on January 6, 1997, without being discharged. The investigator stated that her death was due to progression of her disease and was unrelated to OTFC.

Patient #42905 (AC 200/014) Hospitalization/Death
The following narrative includes events that occured after the original NDA submission.

Patient #42905 was a 56-year-old white male with colon cancer diagnosed in August 1995. He successfully completed protocol AC 200/013 (#32905) and was enrolled in protocol AC 200/014 on March 27, 1996. The patient was using MS Contin 60 mg every 12 hours for around-the-clock control of his cancer pain. OTFC 1200 µg as needed was used for treatment of breakthrough pain. On June 16, 1996, the patient presented with lower extremity edema and was admitted to the hospital for treatment of a deep vein thrombosis. He was started on heparin and Coumadin anti-coagulation therapy. The patient had a history of deep vein thromboses. The patient continued to use OTFC while hospitalized. He was discharged on June 28, 1996. The investigator indicated that this adverse event was unrelated to the use of OTFC.

On September 20, 1996, the patient was admitted to the hospital with renal insufficiency which was rated as severe (BUN was 95 mg/dL the previous