CLINICAL REVIEW

Food and Drug Administration
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Medical Officer Review

Date of Submission:	**November 25, 2002**
Type of Submission:	**Supplement to NDA 19-813 for Pediatric Exclusivity Determination**
Product:	**Duragesic (fentanyl transdermal system)**
Sponsor:	**ALZA**
Review Date:	**April 30 2003**
Medical Officer:	**Dawn Elizabeth McNeil, M.D.**
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Clinical Review for NDA 19-813

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend approval of this supplement.

Duragesic (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic approved for use in persons over the age of 12 years. The current indication is for the management of chronic pain in patients requiring continuous opioid analgesia. The efficacy of Duragesic for this indication was evaluated in the initial NDA submission, 19-813, approved in August 1990. This review evaluated the information presented in the pediatric supplement S036, submitted November 25 2002.

The Sponsor has submitted this supplemental NDA in response to a pediatric written request issued by the FDA.

The sponsor has met the objectives of the written request having demonstrated safe use of the product in pediatric patients as well as a safe and appropriate conversion method to Duragesic from oral and parenteral opioid therapies.

Patients safely initiated therapy with the 12.5 µg/h patch and the 25 µg/h patch. As a 12.5 µg/h patch has not been approved for use, pediatric patients requiring less than 45 mg/day of morphine or an equivalent dose of other opioid would not be appropriate candidates for use of Duragesic.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The lowest strength has clear utility for initiating therapy in pediatric patients. The 12.5 µg/h strength and a dose of 125 µg/h may be confused. It is recommended that in the development of a 12.5 µg/h patch the sponsor should consider making the lowest strength patch distinctive to reduce the risk for error.

(b) (4)

and pursue development of one of these latter patch dosages.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

ALZA submitted a pediatric study request in 1999 to obtain changes to the following sections of the Duragesic label: BOXED WARNING, Clinical Pharmacology (pharmacokinetics subsection), Clinical trials, Precautions (pediatric use subsection), Adverse Reactions, and Dosage and Administration.

In response to this request, the Agency issued a pediatric written request (PWR) on July 15 1999.

Study FEN-USA-87 was submitted to fulfill the requirements of the written request: *A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy*.

The Sponsor submitted safety data from FEN-USA-87, the protocol submitted to fulfill the requirements of the written request, with additional data from studies FEN-INT-24 and FEN-GBR-14. All three of these were open-label studies of the safety and pharmacokinetics of Duragesic in the pediatric patient population. FEN-USA-87, was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years. An initial patch of 12.5 μg/h was to be placed on each subject, with replacement every 72 hours and titration as needed, based on use of rescue medication and pain assessments. FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. Additional pharmacokinetic information was obtained from FEN-FRA-4, an open-label, single dose study in eight patients between the ages of one and five years.

The majority of the pediatric patients who participated in these studies were male (n=176, 60.1 %), and lived outside of the United States of America (n=177, 60.4%). The majority of patients enrolled in studies FEN-USA-87 and FEN-INT-24 were Caucasian, (n=156, 61.9%). No information on ethnicity was collected in FEN-GBR-14. Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years (range 1-16). Two one-year-olds were enrolled in violation of the protocol inclusion criteria, one of whom was included in the youngest age group (2<6 years old). Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males).

The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment. Pediatric patients with either pancreatitis (4%) or sickle cell disease

(4%) represented the next largest groups. Over 70% of the pediatric patients had nociceptive pain (n=189, 71.4%), with the remainder having either neuropathic pain (n=36, 14%) or multiple pain types (n=35, 14%).

B. Efficacy

These studies were all open-label studies without control arms. Efficacy measures were incorporated into the study design to provide descriptive information. The efficacy measures used were the Play Performance Scale (PPS) for evaluation of function, global assessments of pain treatment, pain intensity reporting and use of rescue medication. All of these measures trended towards improvement.

C. Safety

A total of 301 pediatric patients were treated with Duragesic. The eight patients who participated in the single-dose pharmacokinetic study, FEN-FRA-4, were not included in the safety database. The Integrated Summary of Safety (ISS) was based on the experiences of 293 pediatric patients, who received treatment for up to 15 days. Over half (n=234) participated in an extension period during which 172 pediatric patients received Duragesic for more than 16 days but fewer than 61 days and 18 pediatric patients remained on treatment for over 9 months.

With the exception of the 16-18 year old group in which only 44% completed the primary treatment period, over 75% of the pediatric patients per age group completed the study. During the initial treatment period, 38% of the withdrawals were due to death and 22% were due to insufficient response. During the extension phase, 25% of the withdrawals were due to deaths and 17% were due to insufficient response. There were no deaths clearly attributable to study medication.

Over half of the subjects (n=166, 57%) had at least one serious adverse event (SAE). Neoplasm was reported as an SAE in 46% of the pediatric patients who reported an SAE but did not represent a new event. Of the SAEs that could be attributed to study drug, none were unexpected for a product containing fentanyl.

The most common adverse events were fever (38%), vomiting (37%) and nausea (26%). The warning/precautions section of the current Duragesic label notes the theoretical concern that fever could enhance absorption of fentanyl from the patch. In this predominantly immunocompromised study population, while a fever incidence of 38% was noted, no correlation could be found between presence of fever and incidence of adverse effects.

Three patients experienced respiratory depression within 96 hours of beginning Duragesic therapy. Two of the patients died, but there was no evidence that suggested a

causal association between their deaths and the use of study medication. The third patient's decreased respiratory rate resolved after temporary discontinuation of the study drug.

The majority of the patients, 99.5%, were taking at least one other medication. The use of fentanyl in conjunction with CNS sedatives, antiemetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events. These adverse events were generally associated with the reason for the concomitant medications i.e. nausea, vomiting and antiemetics or were known effects of the therapy i.e. nausea, vomiting and chemotherapy.

D. Dosing

Most pediatric patients began treatment with one of the two lowest Duragesic dosage strengths, 12.5 µg/h (an investigational formulation) or 25 µg/h. All patients in FEN-INT-24 started with an investigational formulation of 12.5 µg/h. Patients in FEN-GBR-14 had a minimum starting dose of 25 µg/h.

Patients in study FEN-USA-87 received an investigational formulation of 12.5 µg/h if they had a previous morphine equivalent dose of 30-44 mg. Patients in FEN-USA-87 who had a previous morphine equivalent requirement of 45-134 mg received an initial dose of 25 µg/h.

As there is not currently a 12.5 µg/h patch commercially available, patients requiring less than 45 mg of morphine or equivalent opioid medications are not appropriate candidates for Duragesic therapy.

In the primary treatment period, 41% (n=121) of the participants required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first dose titration during the initial treatment period, 55 (45%) required subsequent dose titration with an average time to subsequent titration of 3.8 days. The titration method, which increased Duragesic by 25 µg/h for each 90 mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

E. Pharmacokinetics

The time to maximal concentration (T_{max}) was shorter in the pediatric subjects. The maximal plasma fentanyl concentration (C_{max}) was 54% higher in the pediatric population.

The elimination half-lives were shorter in the pediatric population than in the adult population. The FEN-FRA-4 study report suggested that the cutaneous depot effect may be less important in the pediatric population.

There was no correlation between fentanyl steady state concentration and adverse events such as nausea, vomiting, fever. In addition, there was no correlation between fentanyl steady state concentration and patient age, gender, race, or Tanner stage for sexual maturity. Alterations in body temperature, location of system application and administration of concomitant medications also had no effect on fentanyl concentrations. The analysis of concomitant medications specifically evaluated the effects of CYP3A4 inhibitors including cimetidine, erythromycin, fluconazole, metronidazole as well as the effects of CYP3A4 inducers such as phenobarbital, dexamethasone and phenytoin and found no effect.

Both steady state concentration and drug clearance were dependent on body surface area, study site and time from dosing. The sponsor reports that "an increase in BSA of 0.1 m^2 is predicted to result in a 4.8% increase in clearance and a 4.6% decrease in steady-state concentration."

F. Special Populations

- Gender

  There were no apparent gender-specific differences in the pharmacokinetics of fentanyl. The overall incidence of AEs was higher among male patients than female patients (94% versus 86%). Although the incidence of malignancy was equal at approximately 70%, a greater percentage of male patients on study USA-87 died (31% vs. 20%). There is no apparent explanation for this finding.

- Race/Ethnicity

  Fever, diarrhea, abdominal pain and nausea were all more common among US subjects and among Caucasians. While Black subjects had an AE incidence of 81%, all other ethnic groups had an AE incidence of greater than 90%. The incidence rates for death were similar for Caucasians, Blacks and Hispanics (29%, 25%, and 21% respectively).

- Other special categories, such as renal and hepatic insufficiency, were not specifically identified and evaluated. Adult patients were not eligible.

Medical Officer Date

Division Director Date

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Duragesic (fentanyl transdermal patch, NDA 19-813), a synthetic phenylpiperidine opioid agonist, is currently approved for the management of chronic pain in patients requiring continuous opioid analgesia.

As a synthetic opioid agonist, fentanyl may be expected to cause the following systemic effects: analgesia, respiratory depression, emetic effects with or without accompanying nausea, antitussive effects, decreased peristalsis and transient hyperglycemia. Opioids have distinct effects on the central nervous system and may cause miosis, increased parasympathetic activity and/or sedation.

Duragesic permits transdermal administration of fentanyl with a dosing interval of 72 hours. The common side effects of Duragesic, as demonstrated in adults, include nausea, vomiting, constipation, somnolence, and diaphoresis. The most serious risk is respiratory depression.

The sponsor currently manufactures four dosage strengths (25 µg/h, 50µg/h, 75µg/h, 100µg/h) approved for use in patients 12 years old and older. The sponsor is not requesting a change in indication but rather is seeking to provide pediatric use information for patients aged 2 years and older.

B. State of Armamentarium for Indication(s)

Fentanyl is currently available in the US as an injectable formulation, as a transdermal patch, and as an oral lozenge. Morphine, hydromorphone, and oxycodone products, in varying formulations, are also marketed for use in patients with chronic pain requiring continuous opioid analgesia. There are no modified-release products approved for patients under twelve years old.

C. Important Milestones in Product Development

June 1984
IND 24, 417 was submitted

August 1990
Duragesic (NDA 19-813) was approved.

October 1998
A meeting was held with DACCADP to discuss proposed development for a lower dose DURAGESIC system and to discuss the requirements for pediatric exclusivity.

February 1999
Letter from DACCADP to ALZA requesting modifications to proposed pediatric study request. Specifically the Division requested inclusion of PK data as well as resolution of issues related to starting dose by age/weight, conversion/titration amounts and patch placement.

March 1999
ALZA submitted a revised pediatric study request.

July 1999

The Agency issued a Pediatric Written Request (PWR) for Duragesic. The requested study was to evaluate the safety and pharmacokinetics of Duragesic in children being treated for chronic pain, who had been using a minimum of 30 mg of oral morphine for one week prior to enrollment i.e. were considered opioid-tolerant. Two hundred children between the ages of two and sixteen years, at least 20% of whom would be appropriate for use of an initial patch size of 12.5 µg/h, should be studied. The PWR specifically stated that children under age 6 should be adequately represented in the study population. The PWR also specified requirements for an initial 72 hours of respiratory monitoring.

November 30 1999
Amendment #1 to the written request

- The number of study subjects was reduced to 150 from 200.
- The requirement for 20% of the subjects to receive an initial patch size of 12.5 µg/h was removed.
- The requirement for additional laboratory testing was removed.
- The submission date was extended from July 1 2001 to December 1 2001.

December 17 1999
Serial number 015 was submitted to IND (b) (4): *A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy (FEN-USA-87).*

February 22 2001
Amendment #2 to the written request
Extension of the submission of pediatric data to "on or before December 1 2002" due to slow study enrollment

July 25 2002
ALZA sent the division an inquiry regarding the adequacy of study representation of children under six years old.

October 1 2002
The Division responded that pediatric patients under the age of six years were adequately represented

D. Other Relevant Information

Duragesic (Durogesic) is marketed in 57 countries and approved for marketing in 64 countries. This product has not been withdrawn from any market due to safety or efficacy concerns.

Duragesic is not currently approved for patients under 12 years old in any market, domestic or foreign.

E. Important Issues with Pharmacologically Related Agents

Drug-drug interactions have been identified with Fentanyl and drugs that inhibit cytochrome P450, isoenzyme 3A4.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No pre-clinical, chemistry or microbiology information was required by the PWR or submitted by the sponsor.

III. Description of Clinical Data and Sources

A. Overall Data

FEN-USA-87 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years, submitted in support of safety and as part of the pooled multiple-dose pharmacokinetic database. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as needed.

FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years submitted in support of safety and as part of the pooled multiple-dose pharmacokinetic database. An patch of 12.5 μg/h (investigational formulation) was placed on each subject, with titration every 72 hours as needed, based on use of rescue medication and pain assessments.

FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study submitted in support of safety. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as needed.

FEN-FRA-4 was an open-label, multi-center, single–arm, nonrandomized pharmacokinetic study in pediatric surgical patients aged between 18 months and 5 years submitted as single-dose pharmacokinetic data.

In total 302 pediatric patients were enrolled in the four studies. One child never received any treatment and was not included in the exposed population (FEN-USA-87). The eight pediatric patients who participated in FEN-FRA-4 were not included in the Integrated Summary of Safety (ISS). As a result the ISS was based on the experiences of 293 pediatric patients

FEN-USA-87:

This study began in March 2000 and is ongoing.

Title: A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy

Objective: Evaluate the safety, dose conversion and titration of Duragesic in pediatric subjects

Population: 200 pediatric patients with at least a one week history of chronic pain requiring scheduled opioids. Subjects were to be enrolled in three age cohorts, a) 2 years to <6 years, b) 6 years to <12 years and c) 12 years to <16 years. Cohorts a and b was to enroll 40 patients each. Cohort c was to enroll 80 patients.

Key Inclusion Criteria:

1. Male or female subjects at least 2 and < 16 years of age with chronic pain of a well documented etiology requiring around the clock opioids who are willing to be hospitalized for the first 48-72 hours of Duragesic treatment. (This criteria was modified to allow home use under supervision, amendment V to the protocol dated 13 November 2000. When at-home subjects would be under constant supervision during the initial 72 hours.)
2. Subjects must have been receiving scheduled opioids for a minimum of 7 days prior to enrollment with a projected need for scheduled opioids for at least the length of the primary 15-day treatment period.
3. Subjects must have been receiving the equivalent of at least 30 mg of oral morphine/day prior to enrollment

Key Exclusion Criteria:

1. Skin disease that could preclude the use of the transdermal system or that could affect local tolerability or fentanyl absorption

2. Known sensitivity to fentanyl, other opioids or adhesives
3. Febrile subjects could be enrolled but serum fentanyl concentrations may theoretically increase…due to temperature dependent increases in fentanyl release and increased skin permeability
4. Life expectancy of less than the length of the primary treatment period (15 days)
5. Subjects whose pain was due to surgery
6. Concomitant treatment with ketoconazole or ritonavir

Study Design: Single-arm, non-randomized, open-label multicenter trial

Study Duration: 15 day primary treatment period with continuation until Duragesic is approved for children or until Duragesic development is stopped

Study conduct:
Opioid tolerant subjects were to be converted from oral/parenteral opioids to Duragesic as follows:

1. The opioid analgesic requirement for the previous 24 hours was to be calculated and converted to the equianalgesic oral morphine dose using the potency conversion table in the current Duragesic label.
2. The oral morphine dose was then to be converted to the appropriate Duragesic dose. A daily intake of 30-44 mg/day of oral morphine was considered appropriate to begin with 12.5 µg/h of Duragesic. A daily intake of 45-134 mg/day of oral morphine was considered appropriate to begin with 25µg/h of Duragesic. Higher doses were to be converted at a ratio of 12.5 µg/h Duragesic for every 45 mg/day of oral morphine.

Duragesic was to be replaced every 72 hours with titration as necessary. Titration was to be based on a conversion of 12.5 µg/h Duragesic for every 45 mg/day of oral morphine equivalent of rescue medication. There was to be a maximum of a 25µg/h increase in Duragesic every 72 hours. Rescue medication usage was to be monitored and recorded for each subject.

Outcome Measures:
Efficacy

- Global assessment-categorical (parent)
- Pain level
  - Vertical visual analog scale (patients 6 years and older)
  - Numeric pain intensity scale (parent/guardian)
  - Scores recorded twice daily by patient and guardian.
  - Additionally, parent/guardian will record pain level at time of rescue use, and one hour later.
- Play performance scale (PPS)
- Child Health Questionnaire
- Rescue medication usage

Pharmacokinetics
Four or five samples per patient for pharmacokinetic analysis

Safety

Vital signs were to be monitored throughout the trial. Respiratory rate and sedation level were to be monitored during the initial 72 hours after application of the Duragesic patch. Bradypnea was defined as a RR < 12 in a 2-6 year old, RR<10 in a 7-10 years old, and RR<8 in a 11 to 16 year old. The combination of bradypnea and excessive sedation were to be recorded as respiratory depression in the CRF. All adverse events were to be tabulated and reported.

Study Results:

Description of patients

The population comprised 199 subjects. The majority were Caucasian (55%) and male (59%). Most of the subjects were preadolescents with a mean age of 10.7 ± 0.28 years. The number of children under 12 years old (48%) was similar to the number of children over 12 years old (41%). Seventy five percent of the subjects were able to start with either a 12.5 µg/h patch (30%) or a 25 µg/h patch (45%).

The subjects had a mean pain duration of 8.3 ±1.3 months, with a median of 1.5 months (range 0.2-120 months). The subjects had a mean baseline pain assessment of 3.7 ±0.3, with a median of 3 (range 0-10 on a numeric pain score scale). All of the pediatric patients had received previous opioid treatment for pain. Seventy percent of the subjects had been taking oral morphine prior to study entry.

Sponsor's summary of Deaths /Discontinuations

The details of deaths and discontinuations, along with further analysis, may be found in the integrated review of safety section.

The majority of the subjects (n=130) completed the initial study phase and entered the extension phase. Twenty-six patients withdrew during the primary treatment phase. Forty-six patients presumably decided not to enter the extension phase, the sponsor has been asked to provide any available reasons for this decision. There were 26 subjects who withdrew during the initial treatment phase. There were 118 subjects who withdrew during the extension phase.

Protocol violations

One hundred forty-five protocol violations occurred during this study, with some pediatric patients having more than one type of violation. One patient was removed from the population due to use of a commercial Duragesic 50 µg/h patch instead of a study patch.

There were eight pediatric patients who did not meet inclusion/exclusion criteria: three were not within the age limits; five did not meet selection criteria NOS. Seven pediatric patients had missing data: seven were missing effectiveness data; three were missing diary data, and three were missing post-baseline data. Eighteen patients had a treatment duration of less than 12 days.

Four pediatric patients had inter-current data violations, representing use of fentanyl or other prohibited medications. There were thirty-one instances of use of other than short-acting opioids.

One hundred twenty seven patients wore their patch over 73 hours, with 22 of them wearing the patch over 84 hours. One hundred nine patients had a treatment interruption of over one hour. Forty-nine patients had a treatment interruption of over 5 hours.

Pharmacokinetics
Pharmacokinetic results will be discussed in Section IV, Pharmacokinetics and Pharmacodynamics.

Efficacy
Efficacy descriptors will be deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to the Section VII of this review, Integrated Review of Safety.

FEN-INT-24:
This trial began June 1999 and ended in September 2001.

Title: A fifteen day trial to document the safety, clinical utility and pharmacokinetics of Duragesic (TTS fentanyl) in the treatment of pediatric subjects with continuous pain requiring opioid therapy.

Objective: To determine the safety, clinical utility and pharmacokinetics of 12.5 µg/h Duragesic in the treatment of subjects aged 2-12 with continuous pain requiring the use of a potent opioid

Population: 40 pediatric patients from 2 to 12 years with chronic pain requiring opioids

Key Inclusion Criteria:
1. Patients between 2 and 12 years old, inclusive
2. Chronic pain of a well documented etiology
3. Pain requiring treatment with a strong opioid that is expected to continue for at least 15 days
4. Prior therapy could include a minor analgesic, weak opioid, or strong opioid equianalgesic to 45 mg of morphine or less/day

Key Exclusion Criteria:
1. History of allergy or hypersensitivity to fentanyl or morphine
2. Active skin disease that precludes application of Duragesic or which may affect the application of fentanyl or local tolerability

3. Life expectancy of less than one month
4. Within 3 days of a surgical procedure
5. Concomitant use of protease inhibitors

Study Design: Open-label, non-randomized multi-center trial

Study Duration: 15 days with an extension period of up to one year

Conduct of Study:
All patients were to begin with a 12.5 µg/h Duragesic patch which was then titrated as necessary. Immediate release morphine was to be allowed as rescue medication. Increases in Duragesic were to be based upon previous opioid usage. Titration was to be based on a ratio of 12.5 µg/h Duragesic for up to 45 mg/day of oral morphine rescue and 25 µg/h if the rescue use exceeded 45 mg of oral morphine. Subjects were not to be given any opioid analgesic except for fentanyl and morphine. Five blood samples were to be obtained for pharmacokinetic analysis.

Outcome Measures:
Clinical Endpoints
- 4-point global assessment scale (categorical)
- 4-point treatment assessment (categorical)
- Play performance scale
- Pain level scale (McGrath Faces and McGill VAS)
- Rescue medication use

Safety, rescue medication use and serum fentanyl concentrations were also assessed.

Study Results:
Description of patients
The 53 subjects enrolled on this study were approximately equally distributed between the genders with 28 male subjects and 25 female subjects. The mean age was 6.5 ± 0.5 years. The majority were younger than 6 years old (55%) and had previous opioid exposure (80%). The majority of these pediatric patients (89%, n=50) had malignancies with pain referable to their tumors or their oncologic treatment. The remainder had non-oncologic illnesses: SSPE (1), Olmsted syndrome (1), metachromatic leukodystrophy (1).

Sponsor's summary of Deaths /Discontinuations
The details of deaths and discontinuations, along with further analysis, may be found in the Integrated Review of Safety. Twenty-seven subjects withdrew from this study. The majority of the discontinuations were due to death (n=11), one of these patients died after withdrawing from the study. Other reasons were insufficient response (n=4), adverse events (n=3), ineligibility to continue the trial (n=3), withdrawn consent (n=1) and "other" (n=5).

Protocol violations
Twenty-five protocol violations occurred during this study, with some pediatric patients having more than one type of violation. In three instances eligibility criteria were not met but the pediatric patients were still enrolled in the trial.

Pharmacokinetics
Pharmacokinetic results will be discussed in Section IV, Pharmacokinetics and Pharmacodynamics.

Efficacy
Efficacy descriptors will be deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to the Section VII of this review, Integrated Review of Safety.

FEN-GBR-14
This study started in March 1996 and ended in October 1998.

Title: A study to assess the safety, efficacy and pharmacokinetics of Duragesic in the treatment of pediatric patients with chronic pain requiring long-term opioid therapy.

Objective:
- To assess the safety, efficacy and pharmacokinetics of Duragesic in the treatment of pediatric patients with continuous pain requiring long-term opioid therapy
- To provide health care professionals with experience of using Duragesic in the treatment of chronic pain requiring long-term opioid therapy

Population: At least 38 pediatric patients with chronic pain requiring opioids

Key Inclusion Criteria:
1. Patients with a confirmed malignancy or other life threatening/terminal disease requiring treatment with a strong opioid
2. Expected to continue to require use of a strong opioid through the course of the study, terminal patients with a life expectancy less than fifteen days were still permitted to enroll
3. Received a stable dose of IR oral morphine or SR morphine for at least 48 hours immediately prior to trial entry. For patients on SR, one or two additional doses of IR morphine did not exclude participation. The minimum daily dose of morphine for entry was to be 30 mg.

Key Exclusion criteria:
1. Allergy or hypersensitivity to morphine
2. Active skin disease precluding use of Duragesic

Study Design: Open-label, non-randomized multi-center trial

Study Duration: 15 days with an extension period of up to one year

Conduct of Study:
Treatment Phase

- Subjects were to be converted from oral/parenteral opioids to Duragesic.
- The minimum starting dose was to be 25 μg/h.
- Duragesic was to be replaced every 72 hours with titration as necessary. Titration was to be done in 25μg/h increments. Rescue medication usage was to be monitored and recorded for each subject.
- The maximum recommended dose was to be 300 μg/h.
- IR morphine was to be provided as rescue medication

Extension Phase

- Indefinite duration
- Efficacy and safety data collected every 2 weeks for the first three months
- Subsequent collection of AE, rescue/concomitant medication use, Duragesic use was to be collected "on an ongoing basis."

Outcome Measures:
Efficacy

- Patient treatment assessment
- Investigator/parent global assessments
- Play performance scale (PPS)
- Disease progression scale
- Rescue medication usage
- Constipation/diarrhea record
- Pain level
  McGrath faces
  Investigator assessment of pain

Safety
All adverse events were to be tabulated and reported.

Pharmacokinetics
A total of 13 blood samples were to be obtained per subject.

Study Results:
Description of patients
The population comprised 41 subjects. The majority were male (73%). Most of the subjects were preadolescents with a median age of 10.5 years. The majority (88%, n=36) had malignancies. The remainder had neurological illnesses: Sanfilippo's syndrome (1), Friedreich's ataxia (1), Duchenne's muscular dystrophy (2) and cerebral palsy/static encephalopathy (1).

Sponsor's summary of Deaths /Discontinuations
The details of deaths and discontinuations, along with further analysis, may be found in the Integrated Review of Safety.

Fifteen subjects discontinued during the treatment phase. Eight were reported to discontinue due to an adverse event. Four had insufficient response and three withdrew consent.

Nineteen withdrew during the extension phase. Nine withdrew due to an adverse event. Two each withdrew due to insufficient response or cessation of symptoms. Three withdrew consent and three withdrew for other reasons.

Protocol violations
Two protocol violations occurred during this study. These pediatric patients received Duragesic despite not having met the minimum dose specified for trial entry, 30 mg/day of morphine. There was no entry dose stated for patient 8. Patient 25 was on a dose of 5 mg of morphine before starting the study.

Efficacy
Efficacy is deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to Section VII of this review, Integrated Review of Safety.

FEN-FRA-4
This study was performed from March 1990 through April 1991, prior to the 1995 black box warning contraindicating the use of Duragesic for postoperative analgesia.

Title: Protocol for pharmacokinetic study of transdermally administered fentanyl in young children

Objective: To study the different pharmacokinetic parameters of transdermally delivered fentanyl for postoperative analgesia in young children without hepatic or renal pathology

Population: Eight pediatric patients. Eight adults aged 30-65 years, undergoing similar types of surgery, were used as controls. These adults were recruited from three French hospital centers.

Inclusion Criteria (only provided for the pediatric patients):
Age 1-5 years and scheduled to undergo a major surgical operation of ≥ three hours

Exclusion Criteria (only provided for the pediatric patients):
1. Weight less than 10 kilos

2. Major deficiency of the respiratory, cardiac, hepatic , renal or central nervous system
3. Intolerance to morphine or fentanyl
4. Opiate dependency
5. Peri-operative blood loss more than or equal to 10% of estimated blood volume

Study Design:
Open-label, multi-center, single-arm, single-dose nonrandomized pharmacokinetic study using adult controls

Study Duration: 144 hours

Conduct of Study:
Duragesic was to be applied to the thoraces of the pediatric patients 2 hours prior to induction of anesthesia.

Postoperatively the patients were to be monitored in a PACU before being transferred to the PICU. While in the PACU, IV morphine could be administered as rescue medication. While in the PICU, SQ morphine could be administered as rescue medication.

Blood for fentanyl levels were to be drawn at the time of patch application, and at 4, 6, 8, 12 hours. The sampling was to be done every 12 hours while the patch was still applied. Samples were to be taken at 4, 6, 12, 24, 36, 48, 60, and 72 hours after the patch was removed.

Study Results:
Deaths /Discontinuations
There were no study discontinuations. There was one study death, an adult with arrhythmia and coagulation disorder. No narrative was prepared for this patient as per the sponsor.

Adverse events
Two of the eight adult subjects had at least one adverse event, as did three of the eight pediatric subjects.

The adverse events reported for the adults were arrhythmia, coagulation disorder and disorientation.

The adverse events reported for the pediatric subjects were respiratory distress, sedation, somnolence and urinary retention.

Pharmacokinetic results
The results of this single dose pharmacokinetic study are discussed in Section IV, Human Pharmacokinetics and Pharmacodynamics.

B. Tables Listing the Clinical Trials

Table 1:
Table listing clinical trials with gender and age information

Trial	Gender		Age in years				
	M	F	<2	2<6	6-12	12<16	16-18
FEN-FRA-4	*	*	1	7	0	0	0
FEN-GBR-14	30	11	0	11	12	11	7
FEN-INT-24	28	25	1	27	21	4	0
FEN-USA-87	118	81	1	27	67	102	2
Total	176	117	3	72	100	117	9

* data not provided

C. Postmarketing Experience

Duragesic is marketed in adults for the treatment of chronic pain requiring opioid analgesia. It is currently approved in 64 countries and marketed in 57 countries (volume 231.2, p.6). It has not been withdrawn in any country due to safety or efficacy concerns.

The original safety database included 510 adult patients (357 acute use/153 chronic use, with over half of the latter using the medication for more than 30 days). The adverse events included nausea, vomiting, constipation, somnolence, and diaphoresis. Respiratory depression was seen in fewer than 5 % of patients: 4% of acute postoperative users and 2% of the chronic users. The current Duragesic label notes the following adverse reactions that were reported post-marketing: edema, tachycardia, weight loss, blurred vision.

FEN-FRA-4 was performed from March 1990 through April 1991, prior to the 1995 black box warning contraindicating the use of Duragesic for postoperative analgesia.

The sponsor searched it's internal pharmacovigilence database for post-marketing reports of AEs in pediatric patients under 16 years old (see appendix A). While a third of the reports were expected adverse events that are included in the adverse reaction section of the Duragesic label, there were other events that were unexpected. For example, there were two instances of inadvertent transfer of the patch from a patient to a child, one of whom died. In addition, there were six instances of abuse: four oral ingestions; two topical applications. The AERS database has fewer than ten reports of Duragesic misuse or abuse in pediatric patients under 16.

D. Literature Review

The sponsor has presented a summarized review of the literature on fentanyl in the pediatric population from January 1 1964 through May 9 2002.

The sponsor cites four pediatric studies in support of the pharmacokinetic data: an abstract; articles based on the findings from FEN-FRA-4 and FEN-GBR-14; a small pilot study done at the (b) (4). Supportive pharmacokinetic studies done in adults were provided as well as articles on the pharmacology of fentanyl (volume 231.7). Multiple studies were cited reporting Duragesic use in pediatric patients.

Two publications have been produced based on the results of the submitted studies.

1. Paut O, Cambouilves J, Viard L, Lemoing JP, Levron JC. Pharmacokinetics of transdermal fentanyl in the perioperative period in young pediatric patients. Anaesthesia 2000; 55: 1192-1212(based on FRA-4)
2. Hunt A, Goldman A, Devine T, Phillips M. Transdermal fentanyl for pain relief in a pediatric palliative care population. Palliative Medicine 2001; 15:405-412 (based on GBR-14)

This reviewer used the following additional references:
Ahmedzai S, Brooks D. et al. Transdermal fentanyl versus sustained release oral morphine in cancer pain: preference, efficacy and quality of life. J of Pain and Symptom management 1997; 13 (5): 254-261)

Noyes M, Irving H. The use of transdermal fentanyl in pediatric palliative care. American journal of hospice and palliative care 2001; 18 (6): 411-16

Collins JJ, Dunkel IJ et al. Trandermal fentanyl in pediatric patients with cancer pain: feasibility, tolerability and pharmacokinetic correlates. Journal of Pediatrics 1999; 134: 319-23

IV. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Fentanyl is a synthetic opioid agonist that interacts primarily with μ-receptors distributed in the brain and spinal cord as well as other tissues. Clinically the principal effects are referable to the central nervous system, where it produces analgesia, sedation and/or drowsiness. While major cardiovascular effects are not usually seen, orthostatic hypotension and syncope have been reported. The effects on urinary smooth muscle are variable with complaints of urinary frequency and urgency both having been reported.

Studies with adults have demonstrated that after an initial gradual increase in fentanyl concentration, peak concentrations occur between 24 and 72 hours after initial application of Duragesic. The concentration of fentanyl measurable in the serum increases over the first few Duragesic applications. After approximately 5 applications, a steady-state serum concentration is reached.

In adults, fentanyl is noted to accumulate in skeletal muscle and fat from which it is released slowly into the blood. Importantly, there is an apparent skin depot effect associated with use of the transdermal fentanyl system. The range of elimination half-life upon cessation of Duragesic use is 13-22 hours as compared to the 3-12 hour half-life range after administration of intravenous fentanyl.

The primary metabolic pathway for fentanyl is the human cytochrome P450 3A4 isoenzyme system. Fentanyl is metabolized through oxidative N-dealkylation to inactive metabolites. Studies done after intravenous administration of fentanyl show predominantly renal excretion of metabolites with less than 10% of the original dose found in fecal matter.

The sponsor derived the information on pharmacokinetics and pharmacodynamics in the pediatric population from study FEN-FRA-4 as well as pooled population pharmacokinetic data from studies FEN-INT-24 and FEN-USA-87, which was used for the pharmacokinetic modeling. FEN-GBR-14 did not provide enough pharmacokinetic samples to allow evaluation.

FEN-FRA-4

Pharmacokinetic analyses

The Duragesic dose in the pediatric patients was 2.5 times that of the adults based on a calculation of µg/kg/h.

As demonstrated in Table 2, the maximal plasma fentanyl concentration (C_{max}) was 54% higher in the pediatric population.

While the time to maximal concentration (T_{max}) was shorter in the pediatric subjects, there was also a wider range of values.

The study report suggested that the cutaneous depot effect may be less evident in the pediatric population.

Table 2:
Fentanyl pharmacokinetic parameters (mean and SD)

	Dose	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-144h} (ng.n/ml)	C_{ss} (ng/ml)	$t_{1/2}$
Children	25 µg/h	1.7 ± 0.66	18 ± 11	87 ± 28	*	14.5 ± 6.2
Adults	50 µg/h	1.1 ± 0.51	33 ± 5	71 ± 28	0.75 ± 0.3	20.6 ± 5.7

* This value was not given since it was only obtained for 2 of the 8 patients.
(volume 231.5/54)

Results from population pharmacokinetics (PPK) analysis (INT-24 and USA-87):

A total of 886 evaluable serum samples, representing 73% of the maximal expected number, were obtained from 242 pediatric patients: 50 subjects from FEN-INT-24 and 192 subjects from FEN-USA-87. Forty of the youngest patients were able to provide

evaluable samples. The only pharmacokinetic data provided by these studies were clearance and steady state concentration. No information on volume of distribution, Cmax, t_{max}, $T_{1/2}$ or AUC could be determined from these studies due to the sparse population pharmacokinetic sampling methods used.

The patient population, presented in Table 3, is not identical to that of the ISS since there are ten fewer patients in the PPK analysis. Ethnicity information was not collected in FEN-INT-24.

Table 3:
Demographics for pediatric patients in pooled pharmacokinetic analysis

	Statistics	All subjects	<6 yrs	6 to <12 yrs	>12 yrs
Wt (kg)	n	241	52	86	103
	Mean ± SD	35 ±19	16 ± 4	29 ± 10	50 ± 19
	Median (range)	31(11-139)	15 (11-26)	27 (14-65)	47 (20-139)
Ht (cm)	n	235	51	86	103
	Mean ± SD	134 ±24	101 ±11	29 ±10	50 ±19
	Median (range)	137 (76-180)	103 (76-123)	27(14-65)	47(20-139)
BSA (m^2)	n	242	52	87	103
	Mean ± SD	1.12 ±0.39	0.67 ±0.1	1.02 ±0.21	1.44 ±0.31
	Median (range)	1.08(0.5-2.4)	0.66(0.5-0.9)	1 (0.6-1.6)	1.45 (0.8-2.4)
Sex	Male	141	28	57	56
	Female	100	24	29	47
Race	White	147	35	53	59
	Hispanic	44	7	16	21
	Black	41	6	13	22
	Asian	3	2	1	0
	Other	6	2	3	1
Race	White	147	35	53	59
	Hispanic	44	7	16	21
	Black	41	6	13	22
	Asian	3	2	1	0
	Other	6	2	3	1

(Table reproduced from volume 231.5/138, where the sponsor notes that the demographic data for one patient was missing at the time of database transfer for PK analysis)

A statistical model was derived with these covariates:

- Study # and site
- Patient demographics (age, gender, race)
- Patient physical characteristics (weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), body temperature, Tanner stage)
- System administration related variables (Time from dosing, system location, dosing gap)
- Concomitant medications (cytochrome P-450 3A4 (CYP3A4) inhibitor or a CYP3A4 inducer)

There was no correlation between fentanyl steady state concentration and adverse events such as nausea, vomiting, fever. In addition, there was no correlation between fentanyl steady state concentration and patient age, gender, race, or Tanner stage for sexual maturity. Alterations in body temperature, location of system application and administration of concomitant medications also had no effect on fentanyl concentrations. The analysis of concomitant medications specifically looked for the effects of CYP3A4 inhibitors including cimetidine, erythromycin, fluconazole, metronidazole as well as the effects of CYP3A4 inducers such as phenobarbital, dexamethasone and phenytoin and found no effect. This may be due to the small number of subjects on these products, given the known effects of CYP3A4 inhibitors in adults.

The sponsor noted that some pharmacokinetic samples were obtained shortly after the first system was applied and others were obtained following a dosing gap, defined as more than one hour between patch removal and patch replacement or the wearing of a given patch for over 72 hours. When these samples were excluded, expected steady state conditions were confirmed.

Both steady state concentration (see Table 4) and drug clearance were dependent on body surface area, study site and time from dosing. The sponsor reports that "an increase in BSA of 0.1 m^2 is predicted to result in a 4.8% increase in clearance and a 4.6% decrease in steady-state concentration. (Volume 231.2, page 10) " The presence of age related differences in clearance in the pediatric population has been evaluated by the Biopharmaceutics reviewer. Refer to the Biopharmaceutics review for further details..

Table 4:
Clearance data from population pharmacokinetics model

	Pediatric data	Adult data
Clearance estimate (CE)	28.1 ±15.32 L/h	28.1 ± 15.32 L/h
CE adjusted for body weight	0.92 ±0.51 L/h/kg	0.77 ± 0.3 L/h/kg
CE adjusted for body surface area	26 ±13 L/h/m^2	19 ± 7 L/h/m^2

After analyzing the data, the sponsor concluded that serum concentrations are not as useful as subjective responses in guiding therapy. The study site effect was thought to be a possible reflection of "demographic differences between the study sites". Due to the large number of sites with a small number of enrolled subjects, demographic difference as a covariate within sites was not evaluated. The sponsor postulates that the study site effect on serum concentrations might be due to "demographic differences between the sites." If the sponsor is aware of or believes that there is a potential for demographic differences in the absorption of fentanyl, this should be studied further. Those further studies would not have to necessarily be done in the pediatric population.

B. Pharmacodynamics

Discussion of pharmacodynamics has been incorporated into the efficacy section of this review.

V. Clinical Review Methods

A. How the Review was Conducted

Volumes 231.1-44 were reviewed in whole or in part, along with the case report tables (CRTs) and Case report forms (CRFs) that were provided as electronic files. The material reviewed for safety in the pediatric population comes from the studies submitted in this supplement as well as the 120-day safety updates provided.

The study protocols, study reports and study results were reviewed for FEN-USA-87 and the other three supporting studies. The ISS was reviewed in depth. The data in the tables was compared with the data in the appendices. Each death was tracked backwards from the ISS through the appendices, narratives, CRTs and CRFs. In addition, data points from a random sample of adverse events were followed through the appendices, CRTs and CRFs.

The sponsor's information on financial disclosure was reviewed.

The AERS database was reviewed for reports of Duragesic related adverse events.

B. Overview of Materials Consulted in Review

The 56 paper volumes submitted in support of this application were reviewed as were the electronic CRF and CRT files.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested by the Division.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

The sponsor has provided financial information from the investigators who participated in FEN-USA-87 and FEN-INT-24, the two studies conducted after implementation of the regulations outlined in 21 CFR Part 54.

The Sponsor was contacted to determine whether there was any record of payments for investigators who did not return financial disclosure forms. The sponsor confirms that no payments were made to the subinvestigators. The sponsor reports having performed due diligence to obtain the missing forms.

FEN-USA-87

The sponsor has submitted financial disclosure form 3455 for the [redacted]. This form was submitted to disclose a significant payment of greater than $25,000 from the trial sponsor to [redacted] for her work as an overall [redacted] and her site enrolled 5 (3%) patients into FEN-USA-87.

The sponsor has submitted financial disclosure form 3455 for the [redacted]. This form was submitted to disclose a significant equity interest of greater than $50,000 worth of Johnson & Johnson stock held in trust for her children. [redacted] and her site enrolled 2 (1%) patients into FEN-USA-87.

The sponsor has submitted financial disclosure form 3455 for [redacted] enrolled no patients into FEN-USA-87.

Seven of the sub-investigators for FEN-USA-87 did not complete financial disclosure forms (PI's name, # subjects enrolled at the site):

[redacted] subjects enrolled)
[redacted] subjects enrolled)
[redacted] subjects enrolled)
[redacted]
[redacted] subjects enrolled)

The sponsor submitted certification with a form 3454 for the remainder of the FEN-USA-87 Principal Investigators and their sub-investigators.

FEN-INT-24

The sponsor submitted certification with a form 3454 for the FEN-INT-24 Principal Investigators and their sub-investigators. Although the clinical investigators had "not entered into any identifiable, disclosable financial arrangements with Johnson & Johnson or any of its affiliates" according to the provided form 3454, many of the investigators were missing financial disclosure forms at study initiation, at study closure and/or at one year post study follow-up.

Summary

The financial disclosure information for FEN-USA-87 appears adequate based on a review of the provided information. Although one investigator was being paid as a [redacted], the number of patients enrolled by [redacted] (n=5, 3%) is too small to influence the study outcome. The financial disclosure information for FEN-INT-24 is incomplete since only 56% (n=9) of the principal investigators ever provided financial disclosure forms. The financial disclosure status of multiple sub-investigators for this study is also incomplete.

The Sponsor was contacted to determine whether there was any record of payments for investigators who did not return financial disclosure forms. The sponsor confirms that no

payments were made to the subinvestigators. The sponsor reports having performed due diligence to obtain the missing forms.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

These studies were open-label, uncontrolled pharmacokinetic and safety studies. Efficacy measures were used to guide titration and use of rescue medication.

Overall pain intensity scores improved to a small degree over the study period. The global assessments of efficacy were improved from baseline.

Play performance scale ratings (PPS) were improved overall and were positively correlated with better parental and investigator assessments of patch efficacy, side effect profile and convenience. These outcomes, along with the absence of a significant increase in rescue medication usage, suggest that Duragesic provided a measure of analgesia.

In the absence of an appropriately controlled double-blind study, no definitive comments can be made about drug efficacy.

B. General Approach to Review of the Efficacy of the Drug

The protocols for studies FEN-USA-87 FEN-INT-24, and FEN-GBR-14 have been discussed in section III so only study related efficacy descriptions will be given here.

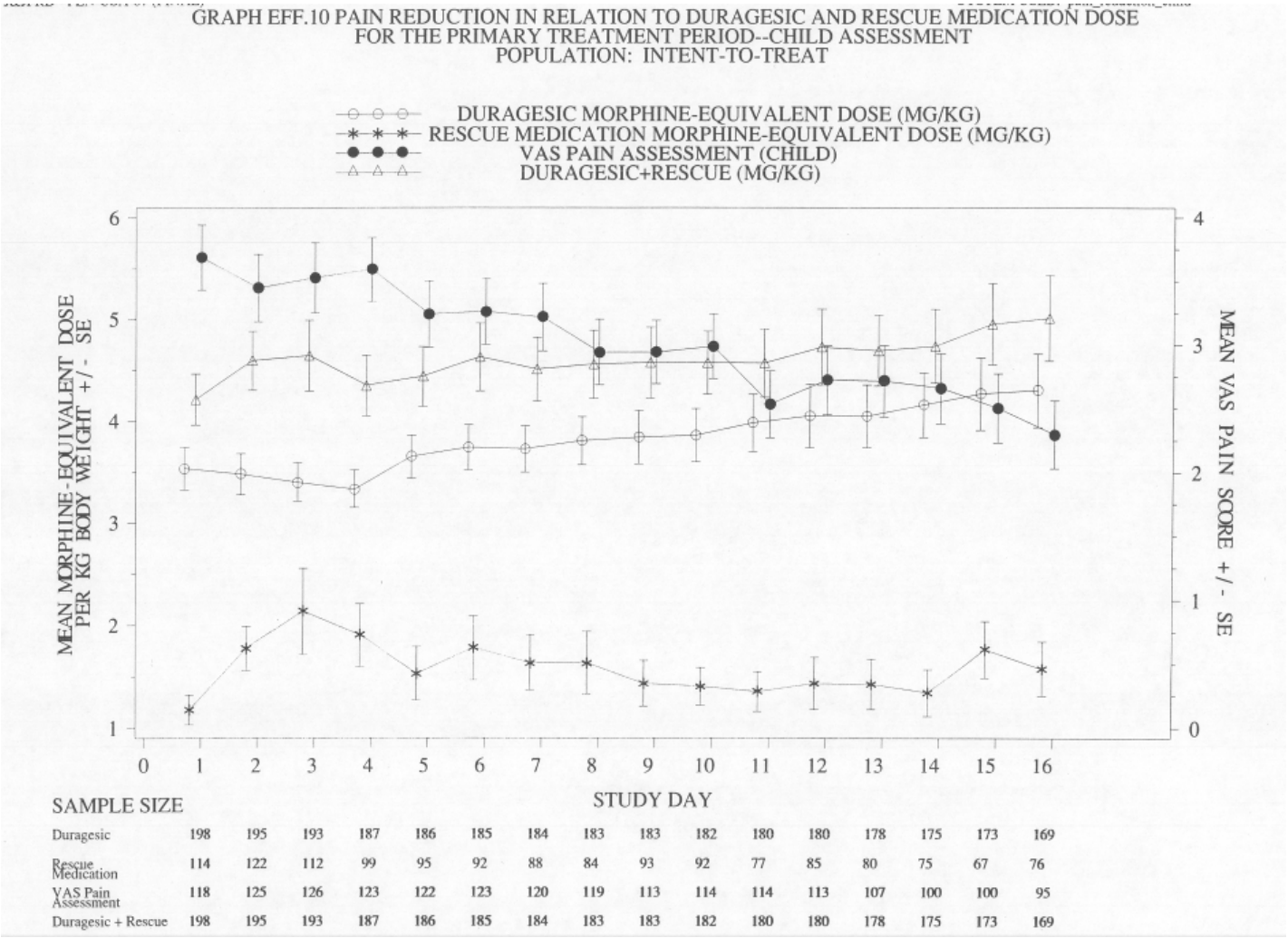
C. Detailed Review of Trials by Indication

FEN-USA-87

Rescue Medication Use

The combined use of Duragesic and rescue was associated with decreased pain intensity according to parental and child reports of VAS scores (see Graph EFF 10 reproduced from sponsor's submission). While the pain intensity plots presented below, based on the data from the primary treatment period of USA-87, cannot be superimposed, the VAS scores are trending downward in both cases. There is noted to be increased use of rescue medication in the first three days, which may reflect the effect of conversion from oral/parenteral treatment to a transdermal formulation. There is also an increase in rescue medication use on day 15, but that may be an artifactual increase based on the decreased sample size.

The use of rescue medication will be further discussed in section VIII, Dosing Regimen and Administration.



Pain level-Parent/Guardian

Of the 199 patients enrolled, 162 were assessed at baseline and 174 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

When the summaries of parental reported average daily pain intensity were assessed, the change from baseline was less than 2 points on a 10 point scale in all measures. The mean pain intensity for the male patients decreased from 3.4±0.3 to 2.4±0.3, with a decrease in the median from 2.9 to 1.4. The mean pain intensity for the female patients decreased from 3.7±0.4 to 3±0.4, with a decrease in the median from 3.9 to 2 (range 0-9.9).

Pain level-Child (age 6-12 years)

Of the 199 patients enrolled, 118 were assessed at baseline and 133 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

When the summaries of patient reported pain intensity were assessed, the change from baseline was less than 1 point on a 10 point scale in all measures. The mean pain intensity for the male patients decreased from 3.5±0.3 to 3.1±0.3. The mean pain intensity for the female patients decreased from 4±0.4 to 3.1±0.5.

Global Assessment

Of the 199 patients enrolled, 189 were assessed at baseline and 149 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

Overall global assessments of pain revealed that the majority of subjects rated their pain treatment as good (34.9%) or fair (30.7%) when measured at baseline. At the treatment endpoint, the majority assessed their treatment as good (34.9%) or very good (52.3%). The proportion of patients rating treatment as good or very good was similar across the evaluated age ranges. While at baseline a smaller percentage of female patients rated their pain control as good when compared to male patients (26.3 % vs. 40.7 %), by the end of the study, the percentages were closer (male patients 33.3% vs. female patients 37.1%).

When baseline assessment was compared with endpoint assessment, 4 pediatric patients (all male) who had originally rated their pain treatment as very good/good lowered their ratings to fair/poor after 15 days of treatment with Duragesic. Fifty-four pediatric patients who initially rated their pain treatment as fair/poor improved their ratings to very good/good at the end of the primary treatment period. The majority of the worsened perceptions of pain treatment took place in the pediatric patients under 12 years old. The improved perception of pain treatment was fairly evenly split between pediatric patients under and over 12.

Play Performance Scale (PPS)

A play performance scale (Table 5) was used to evaluate the subjects' level of daily functioning.

Of the 199 patients enrolled, 180 were assessed at baseline and 171 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

At the end of the primary treatment period, the parents of 75 subjects rated the patch as very good; these subjects had a mean PPS score of 61.5±3. The subjects whose parents rated the patch as poor had a mean PPS score of 12.5±3.

The pediatric patients with a higher average daily Duragesic dose (morphine equivalents >4 µg/h/kg) had consistently lower PPS scores than pediatric patients who had a lower Duragesic requirement (morphine equivalents 0-4 µg/h/kg). However, the mean and median PPS scores showed improvement from Day 1 of therapy in all groups (see Table 6).

Table 5:
Play performance scale

Normal range of play 100-fully active, normal 90-minor restrictions in physically strenuous play/activity 80-active but tires more easily
Mild to moderate restriction of play 70-both greater restrictions of, and less time spent in activities/active play 60-up and around, but minimal active play, keeps busy with quieter activities 50-gets dressed but lies around most of the day; no active play; able to participate in quiet play
Moderate to severe restriction of play 40-mostly in bed, participates in quiet activities 30-in bed; needs assistance even for quiet play 20-oftern sleeping, play entirely limited to very passive activities 10-no play, does not get out of bed 00-unresponsive

Table 6:
PPS scores divided by morphine equivalent dose/day

Morphine equivalents (# of subjects)	Mean PPS score	Median PPS score
Day 1		
0-2 µg/h/kg (61)	44.92 ± 3.05	50
2-4 µg/h/kg (70)	41.71 ± 2.8	40
>4 µg/h/kg (48)	35.42 ± 2.73	40
Day 16		
0-2 µg/h/kg (43)	61.86 ± 3.28	60
2-4 µg/h/kg (41)	61.46 ± 4.02	60
>4 µg/h/kg (48)	51.25 ± 3.47	50

(231.13/59)

When PPS scores were evaluated in the setting of the decision to continue or discontinue the study, the pediatric patients who completed the study began with a mean PPS score of 43±1.8 and ended with a PPS score of 55 ±2. Those pediatric patients who did not complete the initial treatment period had worse PPS score at baseline, 29 ±4, with an average last recorded PPS score of 35±5. The mean final score reflected an improvement but it was still lower than the baseline score for the pediatric patients who did complete the treatment period.

Child Health Questionnaire (CHQ)

This questionnaire was completed by patients aged 10 to 16. The parent questionnaire was used in patients aged 5-16. The CHQ uses a four week recall period so it was collected once at baseline and then monthly during the extension phase.

There are no comparative values for patients who withdrew during the primary treatment period, declined participation in the extension phase, or did not complete the questionnaire.

At the end of the first month, parents reported improvement compared to baseline in the following domains: mental health, family activity, physical, emotional behavior and physical role. On average, patients reported improvement in bodily pain, physical role and physical functioning.

FEN-INT-24

Rescue medication use

The use of rescue medication will be further discussed in section VIII, dosing, regimen and administration. Overall the amount of rescue was fairly constant through the trial.

Pain intensity assessed by the investigator

The assessment of pain intensity was limited to the primary treatment period. Of the 53 patients enrolled, 53 assessments were available at baseline and at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority of the patients had pain described by the investigator as moderate (40%) or severe (32%) at baseline. At the endpoint, the majority had no pain (57%) or mild pain (14%) perceived by the investigator.

Pain intensity scale (McGrath Faces)

The collection of pain level scale information was limited to the primary treatment period. Of the 53 patients enrolled, 47 baseline assessments were available and 51 assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The mean baseline score was 2.3 with a standard error of 0.2. At the endpoint, the mean score was 1.3 with a standard error of 0.3. There were no differences by age or gender.

Pain intensity scale (McGill VAS)

The collection of pain level scale information was limited to the primary treatment period. Of the 53 patients enrolled, 47 baseline assessments were available and 49 assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The mean baseline score was 38.2 with a standard error of 4.02. At the endpoint, the mean score was 25.4 with a standard error of 4.53. While there were baseline differences by age and gender, there were no differences at the endpoint.

Global assessment of pain control

The global assessment of pain control was limited to the primary treatment period. Of the 53 patients enrolled, 41 parental assessments were available and 45 investigator assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority of the investigator's assessments were excellent (42%) or good (31%) with 9% rated as poor. The parental assessments were similar with 44% rating pain control as excellent, 32% rating it as good and 12% each rating pain control as fair or poor.

Treatment assessment

The treatment assessment was limited to the primary treatment period. Of the 53 patients enrolled, 46 were assessed at baseline and 47 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority rated their pain treatment as fair (41%) or poor (24%) at baseline. At the end of the primary treatment period, the majority rated their pain as good (47%) or very good (30%). The majority of the subjects whose pain had originally been rated as poor/fair at baseline improved their assessment to good/very good by the endpoint (64%). One subject whose baseline assessment had been good/very good worsened his rating to poor/fair.

Play performance scale (see Table 5)

The play performance scale ratings in study INT-24 ranged from 59/100 to 68/100 at the final assessment. The average change from baseline was 44 points. There were no significant differences in the ratings when analyses by age and by gender were performed.

When the play performance scores were evaluated by the level of treatment satisfaction, there was a marked difference between the group who rated the patch as unsuccessful and the group which rated the patch as successful. The former group had a Day 16 mean play performance score of 22.5 (a decrease of 14 points from baseline), while the latter group had a Day 16 mean play performance score of 69.6 (an increase of 28 points from baseline).

As would be expected, when the PPS score was evaluated in the context of the daily average pain scores, patients with less pain had higher PPS scores. However, all pediatric patients had increased PPS scores on Day 16. The pediatric patients with the most pain, i.e. those with VAS >50-100, had a mean score of 43.3 (a 9.2 point change from baseline). The pediatric patients with mild-moderate pain, i.e. those with VAS 10-50, had a mean score of 48.6 (an 8.1 point change from baseline). The pediatric patients with no pain had a mean score of 77.5 (a 21.5 point change from baseline).

A review of PPS score by patch dose revealed that PPS score in pediatric patients receiving the 12.5 µg/h patch was consistently higher throughout the trial than the PPS score in pediatric patients receiving patches in any of the higher strengths. This may reflect the effect of worse pain and/or disease progression in pediatric patients requiring more than 12.5 µg/h for pain control.

FEN-GBR-14

Rescue medication usage

The use of rescue medication will be further discussed in section VIII, dosing, regimen and administration. Overall the amount of rescue was fairly constant through the trial.

Patient treatment assessment

Of the 41 patients enrolled, 25 assessments were available on Day 3 (the first day recorded) and on Day 15.

At the initial assessment, the majority of parents rated the patch as good (49%) or very good (17%). At the Day 15 assessment, the majority of the parents still rated the patch as good (56%) or very good (28%).

Play performance scale (PPS)

The median PPS score started at 50 and remained at 50 through the trial.

Pain intensity (McGrath faces)

The letter pain scores were converted to a numerical score with 0 being the best and 1 being the worst. A score of 0.59 (category E) or below was considered an acceptable pain level. A score above 0.59 was unacceptable. The ratings were done twice daily. On day 0, eleven subjects had one unacceptable pain rating and seven had two unacceptable pain ratings. On Day 15, four had one unacceptable pain level and one had two unacceptable pain levels.

Investigator/parent global assessments

The majority of the investigators (67.5%) had the impression that the treatment was good or very good by day 15. The majority of the parents agreed, with 70% rating the treatment as good or very good.

Disease progression scale

The majority of the subjects (68%) showed deterioration over the study period.

Constipation/diarrhea record

Seventeen subjects noted loose bowels on day 0, only eight noted this on day 15. Eight complained of constipation on day 0, three had this complaint on day 15.

D. Efficacy Conclusions

These studies were all open-label investigations so they cannot provide evidence of drug efficacy.

Pain intensity as determined by parents or guardian showed a change of less than 20%. The pain intensity levels as measured by the patients changed less than 10%.

The majority of patients, physicians and parents/guardians gave the treatment a global assessment rating of good or very good/excellent.

There was a clear positive correlation between higher play performance scores and treatment satisfaction. Children with low play performance scores had higher pain intensity ratings and lower global assessments.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Duragesic may be used safely in the pediatric population. The adverse events seen in the pediatric trials mirrored the adverse events documented for the adult population.

There were 94 deaths during these trials. There was no clear correlation between use of study drug and death in any of these patients, many of whom (97%) had underlying malignancies.

Serious adverse events (SAE) occurred in over half (57%) of the participants in these trials, with neoplasm being the most commonly reported.

The common adverse events during these trials were nausea, vomiting, constipation, somnolence, and diaphoresis, comparable with the adverse events seen in the adult patient population using Duragesic. The incidence of these adverse events remained steady over the primary and extension periods.

The majority of the patients were taking at least one other medication while on study-99.5%. The use of fentanyl in conjunction with CNS sedatives, antiemetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events.

The emergence of opiate withdrawal symptoms on conversion from morphine to fentanyl has been reported in adults. Few pediatric patients reported withdrawal symptoms during the trials. It should be noted that these symptoms may occur in conjunction with adequate pain control.

B. Description of Patient Exposure

Demographics

The Integrated Summary of Safety (ISS) database, comprising 293 patients, represented results from three studies: FEN-USA-87, FEN-INT-24 and FEN-GBR-14. The majority of the pediatric patients (see Table 7) who participated in these studies were male (n=176, 60.1 %), Caucasian, (n=156, 61.9%) and lived outside of the United States of America (n=177, 60.4%).

Table 7:
Demographics for the ISS

	Statistics	All subjects
Age in years	n Mean Median (range)	293 9.7 10 (1-18)
Ht (cm)	n Mean Median (range)	280 133.8 137 (69-181)
Wt (kg)	n Mean Median (range)	290 34.9 31 (7-139)
Sex	Male Female	176 117
Race	White Hispanic Black Asian Other	156 45 41 4 6

Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years. Two one-year-old pediatric patients were enrolled in violation of the protocol inclusion criteria. One was erroneously included in the youngest age group (2-6 year olds), the other was not included in the analyses by age category since she was under 2 years old. Nine patients were $\geq$16 years old from study FEN-GBR-14. Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males).

The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment (see appendix B). All patients with pain related to oncologic treatment, such as chemotherapy related mucositis were reclassified by this Reviewer as having pain due to malignancy. Pediatric patients with pancreatitis (4%) and pediatric patients with sickle cell disease (4%) represented the next largest groups of patients. A detailed list of the diagnoses for the trial participants is given in appendix B.

Over 70% of the pediatric patients had nociceptive pain (n=189, 71.4%), with the remainder having either neuropathic (n=36, 14%) or multiple pain types (n=35, 14%). The duration of pain ranged from one day to ten years in the combined population from studies FEN-INT-24 and FEN-USA-87, with a mean of 6.8 months (volume 231.2, p.16). The pediatric patients in study INT-24 had a mean of 1.3 months (±0.42) of continuous pain.

Subject disposition

A total of 301 pediatric patients were treated with Duragesic. All three studies began with a fifteen day study treatment phase followed by an extension phase. With the exception of the oldest patients, >75% of patients in each age group completed the trial (see Table 8).

Table 8:
Pediatric patients who completed the primary treatment period by age and study group

Age in years	<2	2<6	6<12	12<16	16-18
FEN-GBR-14	0	7 (64%)*	7(58%)	9 (82%)	3 (43%)
FEN-INT-24	1 (100%)	17 (63%)	15 (71%)	3 (75%)	0
FEN-USA-87	0	25 (93%	55 (82%)	92 (90%)	1 (50%)
All	100%	75%	77%	89%	44%

*The percentages given are the percentage of patients in a given age group.

While 80% (n=235) of the population completed the primary treatment period, only 58% (n=171) of the population entered the extension phase. The majority of the patients in these studies had fewer than sixty days of Duragesic exposure (see Table 9).
As of the ISS cutoff date of November 25 2002, 12 patients on FEN-USA-87 were receiving ongoing Duragesic treatment.

Table 9:
Duragesic exposure by time interval

Time Interval	Original ISS n(%)	120 day update n(%)
Total number of subjects	293	293
0-72 hours	15 (5.1)	15 (5.1)
>72 hours-15 days	44 (15)	44 (15)
16-30 days	136 (46.4)	125 (42.7)
31-60 days	48 (16.4)	47 (16.0)
61-90 days	11 (3.8)	11 (3.8)
91-120 days	14 (4.8)	13 (4.4)
121-270 days	16 (5.5)	20 (6.8)
>270 days	9 (3.1)	18 (6.1)

(table reproduced from ISS safety update 234.1/75)

The sponsor was asked to provide the reasons for failure to enter extension phase. The sponsor responded that the decision to enter the extension phase was a matter of individual discretion. The CRFs did not capture reasons for the decision not to continue.

There were 58 withdrawals during the primary study treatment period, a detailed list is provided in Appendix C. The investigators in study FEN-GBR-14 classified death as an adverse event. Deaths have been separated out by this Reviewer to form a discrete category in Table 10 so the deaths reported in GBR-14 have been reclassified. The majority of the withdrawals in the primary treatment period were due to death (n=22). The next largest group was patients complaining of insufficient response (n=15). One patient withdrew consent because he did not want to stay in the hospital. One child was withdrawn from the study due to impending discharge from the hospital. This last case was originally classified under category other, and was moved to ineligible to continue trial.

There were 139 withdrawals during the extension treatment period, a detailed list is provided in Appendix C. The deaths reported in GBR-14 have been reclassified as previously stated. Two patients who left the country were originally classified as other but were reclassified as ineligible to continue the trial. Sixteen patients complained of insufficient response, this category includes patients who had to change to another analgesic for better pain management, and those who needed more frequent patch changes then allowed by the protocol. Seven patients had consent withdrawn for reasons such as wishing greater flexibility in patch management or " tired of collecting data."

Table 10: Subject disposition

	Disposition	USA-87	INT-24	GBR-14
Began treatment	293	199	53	41
Completed 15 day study treatment period	235 (80%)	173	36	26
Withdrawals during study treatment period	58 (20%)	26	17	15
Death	22 (38%)[a]	6	8	8
Adverse event other than death	8 (14%)[a]	6	2	0
Withdrew consent	4 (7%)[a]	1	1	2
Insufficient response	13 (22%)[a]	5	3	5
Decreased need for opiate	5 (9%)[a]	2	3	0
Patient noncompliance	2 (3%)[a]	2	0	0
Ineligible to continue trial	3 (5%)[a]	3	0	0
Other	1 (<1%)[a]	1	0	0
Did not enter extension treatment period	64 (27%)[b]	43	18	3

Table 10: Subject disposition (continued)

	Disposition	USA-87	INT-24	GBR-14
Entered extension treatment period	171(58%)	130	18	23
Discontinued**	139(81%)[a]	104	15	20
Death	42 (30%)[a]	26	6	10
Adverse Event	13 (9%)[a]	12	1	0
Withdrawal of consent	13 (9%)[a]	10	0	3
Insufficient response	23 (17%)[a]	17	2	4
Decreased need for opiate	24 (17%)[a]	21	1	2
Patient noncompliance	2 (1%)[a]	1	0	1
Ineligible to continue trial	19 (14%)[a]	15	4	0
Using commercial Duragesic	12 (9%)[a]	11	1	0
Other	5 (4%)[a]	5	0	0
Completed (GBR-14, INT-24)	6	0	3	3
Ongoing (USA-87)	12	12	0	0

(data derived from volumes 231.2, 231.8, 231.29, 231.31, ISS update) *Three additional pediatric patients in FEN-GBR-14 did not receive Duragesic despite entering the extension treatment period

[a] The percentages represent the percentage of patients who withdrew for a given reason

[b] The percentage represents the percent of patients eligible to continue who chose not to do so

C. Methods and Specific Findings of Safety Review

Summary

In addition to the ISS, the Sponsor provided a table with safety data from the pharmacokinetic study FEN-FRA-4, which was done prior to the black box warning contraindicating use of Duragesic in the management of postoperative pain. The black box warning was added because of the occurrence of two deaths when Duragesic was used in opioid-naïve postoperative patients.

Two of the eight adult subjects, in Study FEN-FRA-4 had at least one adverse event, as did three of the eight pediatric subjects. The adverse events reported for the adults were arrhythmia, coagulation disorder and disorientation. The adult subject with the first two adverse events died. The adverse events reported for the pediatric patients were respiratory distress, sedation, somnolence and urinary retention.

The ISS includes pooled results from studies FEN-USA-87, FEN-INT-24 and FEN-GBR-14, for a total of 293 patients. FEN-INT-24 and FEN-GBR-14 were completed at the time of initial submission so that submission included complete safety data from the primary treatment period as well as the extension period. For FEN-USA-87, all data accumulated from the primary treatment period are included as well as data from persons who entered and ended the extension period on or before 3 March 2002. The data for persons ongoing in study FEN-USA-87 are complete through 25 November 2002. As previously discussed

the safety data from FEN-FRA-4, a single dose pharmacokinetic study, were not integrated into the ISS.

The majority of subjects (91%) had adverse events reported. Nausea and vomiting were the most common specific adverse events during both periods, other than non-treatment emergent neoplasm. Overall incidence of AEs was higher during the primary study treatment period than during the extension period.

Deaths

The ISS and 120-day safety update report 94 deaths, tabulated in Appendix D. The death of subject A30064 (FEN-USA-87), a six year old with metastatic neuroblastoma, was recorded as an SAE and coded as doubtfully related to treatment by the investigator. The other 93 deaths were all coded as not related to treatment. The majority of deaths (n=87, 92.6%) occurred during treatment or within thirty days of treatment cessation. Seven deaths occurred more than thirty days after treatment. The sponsor notes that five deaths in study FEN-GBR-14 were not included in the database since they occurred more than thirty days after cessation of therapy and were considered unrelated to treatment.

The majority of the deaths in the primary treatment phase and the extension phase were due to progression of underlying malignancies. There were three cases, summarized below, with a possible correlation to use of study medication. In all three instances, the primary investigator did not feel that there was a correlation between study drug and the involved subject's demise. A review of the narratives and case report forms did not suggest a correlation between death and use of the study medication but the information provided was insufficient to make a definitive determination..

- GBR-14/029: A 16 year old (Friedrich's ataxia) with a past medical history significant for dysphagia, aspiration and dyspnea. Within (b) (6) day of beginning study medication, he had an episode of emesis with aspiration, and subsequent cyanosis. He died that day. While fentanyl induced nausea/vomiting could have played a role in his demise, his known history of prior aspiration episodes makes it unclear what role, if any, study drug played in his death.
- GBR-14/069: A 17 year old (relapsed acute lymphoblastic leukemia) who had just completed a five day course of chemotherapy. (b) (6) after placement of the study medication, he vomited and subsequently had a cardiac arrest. While fentanyl induced vomiting with subsequent aspiration could have played a role in his death, the history of recent chemotherapy administration might have made him more likely to experience episodes of nausea/vomiting. While it is possible that study drug contributed to his demise, it is improbable given the short duration of study drug exposure.
- INT-24/A30096: A 3 year old (sub-sclerosing panencephalitis) was described as experiencing encephalopathic changes, peripheral edema and agitation on Day (b) (6) of therapy. On the day of her death, day (b) (6) her medication was increased from 200µg/h to 300µg/h. While it is possible that the increase in study drug contributed to her demise, it is improbable given the short duration of exposure to the increased dosage.

Of the deaths that occurred in patients off study, the majority were due to progression of underlying malignancies. Most occurred more than 4 days after the last use of study medication, which would allow for the passage of five drug half-lives. There were four cases that occurred within four days of the last use of the study medication. In all instances the primary investigator did not feel that there was a correlation between study drug and the involved subject's demise. A review of the narratives and case report forms failed to provide evidence of a causal relationship between the patient's death and use of study drug.

- USA-87/A30065: A 9 year old (osteosarcoma) who withdrew from the trial due to severe pain after 28 days of therapy. He died (b) (6) days after withdrawing from the trial.
- GBR-14/33: A 12 year old (glioma) who withdrew from the trial due to severe pain after 21 days of therapy. He died while receiving diamorphine infusions, (b) (6) days after withdrawing from the trial.
- GBR-14/44: A 4 year old (rhabdomyosarcoma) who withdrew from the trial due to severe pain after 21 days of therapy. He died while receiving diamorphine and midazolam infusions, (b) (6) days after withdrawing from the trial.
- GBR-14/105: A 6 year old (neuroblastoma) who withdrew from the trial due to uncontrolled pain after 14 days of therapy. He died while receiving diamorphine, levomepromazine and midazolam infusions, (b) (6) days after withdrawing from the trial.

Serious Adverse Events (SAE)

Over half of the subjects (n=166, 57%) in the population of 293 patients had at least one SAE, with neoplasm being the most common (see table 11, a complete list of SAE is presented in Appendix E). Neoplasm was reported as an SAE in 46% of the pediatric patients but did not represent a new event for any of these patients. Fever, granulocytopenia, and pain were the most common serious adverse events, which is not unexpected in this population of children with malignancies.

Table 11:
Incidence of specific SAE occurring in >5% of subjects

Number with at least one SAE	166 (57%)
Neoplasm	77 (46%)
Fever	31 (19%)
Granulocytopenia	15 (9%)
Pain	14 (8%)
Vomiting	11 (7%)
Dyspnea	9 (5%)
Respiratory Insufficiency	9 (5%)
Thrombocytopenia	8 (5%)
Sepsis	8 (5%)
Anemia	8 (5%)

Modification of table ISS update AE.13AB. The percentages given are the percentage of the 166 patients who experienced at least one SAE.

Neoplasm (46%), fever (19%), granulocytopenia (9%), pain (8%), vomiting (7%) respiratory insufficiency (5%), and dyspnea (5%) were all reported as SAE during these trials. These adverse events can be associated with malignancy and other terminal illnesses.

While no cases of neoplasm resolved after stopping Duragesic, in many cases (see subsection entitled deaths) patients had worsening of their underlying malignancies while on therapy. Further details about patients' responses to adverse events may be found in the subsection entitled adverse events of special concern.

Discontinuations due to adverse events

A total of 197 patients withdrew during the treatment period, as shown in Table 10. The majority of discontinuations were due to death (n=64, 32%). Discontinuations for reasons other than death or adverse event are tabulated in Appendix C. Twenty-one patients withdrew due to adverse events, as shown in Table 12 below.

There were 5 patients who withdrew due to adverse events definitely related to use of study drug. These adverse events included application site reaction, somnolence/sedation, fatigue/slurred speech/mental slowness, obstipation and pain/anxiety with patch removal.

There were 4 patients who withdrew due to adverse events possibly related to use of study drug. These adverse events included lactic acidosis/altered mentation, agitation, fever/nausea/vomiting/headache, and pruritis/skin abrasions.

The other patients withdrew for reasons that were unrelated to use of study drug, insofar as can be determined from review of case report forms.

Table 12:
Patients who withdrew due to adverse events

Study / Patient #	Age/sex	Adverse event (s)	Study day	Dose
USA-87 A30020	15/F	Application site reaction	28	0.21 µg/kg/h
USA-87 A30025	12/F	Bone marrow transplant	24	2.64 µg/kg/h
USA-87 A30079	14/M	Somnolence/sedation	12	0.19 µg/kg/h
USA-87 A30088	15M	Irritability/Nervousness	63	0.42 µg/kg/h
USA-87 A30094	15/F	Loss of appetite	74	1.19 µg/kg/h
USA-87 A30110	2/F	Abdominal pain, mucositis	56	0.83 µg/kg/h
USA-87 A30186	3/F	Lactic acidosis, Altered Mentation	26	0.83µg/kg/h

Table 12:
Patients who withdrew due to adverse events

Study / Patient #	Age/sex	Adverse event (s)	Study day	Dose
USA-87 A30203	15/F	Agitation	2	0.88 µg/kg/h
USA-87 A30321	15/M	Pulmonary edema	13	0.56 µg/kg/h
USA-87 A30335	10/F	Typhilitis	27	0.78 µg/kg/h
USA-87 A30367	13/F	Erythema gangrenosum	17	0.81 µg/kg/h
USA-87 A30389	15/M	Pruritis/Skin abrasions	9	0.52 µg/kg/h
USA-87 A30396	13/F	Renal insufficiency	19	1.02 µg/kg/h
USA-87 A30406	15/M	Fever/Nausea/Vomiting/Headache	13	0.64 µg/kg/h
USA-87 A30504	14/F	Focal seizure	30	0.31µg/kg/h
USA-87 A30536	12/F	Cerebral hemorrhage/fever/loss of consciousness/tremor/vomiting	3	0.96 µg/kg/h
USA-87 A30535	6/M	Loss of consciousness/ Cerebral hemorrhage	32	2.78 µg/kg/h
INT-24 A30004	4/F	Pain/anxiety with patch removal	22	11.77 µg/kg/h
INT-24 A30076	5/F	Fatigue/Slurred speech/mental slowness	3	1.09 µg/kg/h
INT-24 A30086	5/F	Obstipation *opioid naïve patient*	9	0.78µg/kg/h
GBR-14 058	2/M	Night awakening/ Insufficient resp	7	2.17 µg/kg/h

Adverse events

While 90% of subjects reported at least one AE during treatment, fever and/or vomiting were reported by approximately one third of patients. The incidence of AE reported by >2% of subjects in either the primary or extension treatment period is displayed in Appendix F.

Neoplasms and hematological disorders were reported as adverse events, in this population of pediatric patients with pre-existing solid and hematological malignancies. Since the neoplasms and hematological disorders did not represent treatment-emergent events it is difficult to assess what casual role, if any, Duragesic had. Additionally hospitalizations for chemotherapy were reported as adverse events. Since the pediatric

patients had known malignancies, it is improbable that Duragesic played a role in these scheduled hospitalizations.

The investigators considered the following to be related to trial medication: nausea and vomiting, diaphoresis, confusion, agitation, constipation, pruritis, somnolence, headache, and application-site reaction. With the exception of application site reactions, these adverse events are all expected complications of malignancies and terminal diseases in children. In light of this fact, it is not possible to apportion causality of these adverse events to use of study drug versus underlying disease.

There was no trend towards increase or decrease in adverse events over time when duration of Duragesic exposure was assessed. The number of affected individuals with a given AE of any severity, by duration of exposure, is shown in Table 13.

Table 13: Incidence of AE occurring in >5% of subjects by duration of exposure

	Duragesic								
	Duration of exposure								
	Total n=293	0-72 hours n=293	>72 hours-15 days n=278	16-30 days n=234	31-60 days n=109	61-90 days n=62	91-120 days n=51	121-270 days n=38	>270 days n=18
# of affected subjects	268	163	220	119	77	37	30	31	12
Vomiting	98	39	45	21	13	5	2	2	1
Nausea	69	19	38	12	8	2	4	2	0
Abdominal Pain	43	8	26	7	5	2	2	0	1
Constipation	38	7	19	5	5	3	1	4	2
Diarrhea	37	6	17	7	4	3	1	0	0
Fever	103	35	46	21	13	3	1	6	0
Pain	39	5	20	7	8	0	1	2	1
Edema	18	4	9	2	4	2	0	0	0
Dyspnea	17	0	11	3	0	1	1	1	1
Headache	47	9	23	7	5	3	1	5	1
Pruritis	39	13	22	5	3	1	0	1	0
Rash	20	4	12	2	1	0	0	0	1
Somnolence	21	8	9	2	3	0	0	0	1
Insomnia	20	3	8	2	5	2	0	1	1
Infection	19	2	5	6	4	1	2	2	1
Neoplasm	69	11	17	14	16	4	7	11	1
Thrombocytopenia	34	10	18	8	6	1	1	1	0
Site Reactions	19	3	11	2	4	0	0	0	0

Modification of sponsor's table AE.06B(The numbers given are the number of affected individuals)

Appendix F displays the incidence of AE, of any severity, occurring in >2% of subjects in either primary or treatment phase. The AEs that occurred in under 2% of subjects are tabulated in Appendices G and H. There was no clear association of AE with Tanner

sexual maturity rating. There was no correlation between patch placement and adverse events. Patches were applied to the upper arm, chest, upper and lower back, abdomen, and leg among other areas. However, in a few pediatric patients (n=19) who wore the patch on their leg, only 52% experienced an adverse event as opposed to the 70-75% of subjects who experienced adverse events while wearing the patch elsewhere on their bodies.

Vital signs

The vital signs were not collected uniformly across the three studies. Blood pressure was not collected in studies FEN-INT-24 or FEN-GBR-14. Temperature was not collected in study FEN-GBR-14.

Clinical significance was defined as a change of at least 25% from baseline (see Table 14a). The majority of the patients had changes in respirations (71%). Over half (59%) had a significant change in pulse. These changes could reflect effect of study drug on the cardiovascular system or its analgesic effect. It is not possible to determine which is the case with the information that was provided for review. The mean changes all changed by one unit of measurement or less (see Table 14b).

Table 14a: Vital signs: Subjects with a 25% change from baseline

	Number of subjects ≥25%	Percent ≥25%	Number of subjects ≤25%	Percent ≤25%
Pulse (beats/min)	96	32.8	78	26.6
Systolic Blood Pressure (mmHg)	37	12.6	27	9.2
Diastolic Blood Pressure (mmHg)	76	25.9	60	20.5
Respirations (breaths/min)	122	41.6	86	29.4

Reproduction of table 10:10 from sponsor's ISS update

Table 14 b: Mean changes from baseline

Parameter	Temperature (ºC)	Pulse (BPM)	SBP (mmHg)	DBP (mmHg)	RR (Resp/min)
Studies where collected	INT-24/USA-87	All	USA-87only	USA-87only	All
End of Week 1	0.05 (217)	0.8 (242)	-0.7 (174)	-1.0 (174)	0.2 (246)
End of Primary treatment period	0.05 (195)	0.5 (211)	-0.8 (164)	-1.0 (164)	-0.2 (209)

Note: the number in parentheses represents the number of subjects evaluated (231.38/284)

D. Adverse Events of Special Concern

Adverse events of special concern by age group are displayed in Appendix I. The only noteworthy finding is that the sponsor reported two adolescents with withdrawal symptoms. This reviewer found a wider age range of children with withdrawal symptoms as will be discussed below.

Oral exposure

Due to the known propensity of pediatric patients to put things into their mouths, it was recommended that the patch be placed on the upper back area of the youngest pediatric patients when possible. There were no reports of oral ingestion of the patch by participants in these clinical trials.

Opioid Withdrawal

As these trials attempted to determine the optimal method of dose titration in a predominantly opiate tolerant/dependant population, the possibility of opiate withdrawal during the conversion from oral or parenteral opiates to a transdermal system was a serious concern.

The sponsor reported two pediatric patients with withdrawal syndrome that occurred during treatment (summarized below). Narcotic withdrawal was also reported in subject A 30039 on Day 26 but her last dose of trial medication was on Day 16.

- A 15 year old (pancreatitis, A30418) had withdrawal symptoms deemed nonserious and possibly related to Duragesic. The episode, which lasted 16 days, occurred when the child had been on 25 µg/h (0.34 µg /kg/hr) of Duragesic for 67 days. There was no disruption of Duragesic treatment and the subject was reported to have recovered.
- A 14-year old (pancreatic cancer, GBR-025) had withdrawal symptoms that were deemed nonserious and definitely related to Duragesic. The episode, which was characterized by pain, restlessness and diaphoresis, lasted 1 day. It occurred when the child had been on 150 µg/h (4.77 µg /kg/hr) of Duragesic for 8 days. He had removed the patch before the episode but 5 hours later he "agreed to have it replaced." The replaced system was also 150µg/h but was increased to 175µg/h at the next system application.

In addition to the pediatric patients reported above, on review of the adverse event reports, three other pediatric patients (summarized below) had symptoms consistent with opiate withdrawal on initial patch conversion, although they were not coded as such by the investigators.

- A 15 year old girl (ALL, A30203) had severe agitation along with nausea and diaphoresis on Day 2 of Duragesic treatment with 75µg/h (0.88 µg /k/h).). She had previously been on 96 mg of IV morphine/day, although in the 24 hours prior to starting the study she was given 288 mg morphine. All three events were considered very likely related to Duragesic treatment by the investigator. This subject withdrew from the study as a result of these adverse events. She recovered from this SAE once study drug was discontinued.

- A 15 year old boy (nasopharnygeal carcinoma, A30104) had severe insomnia and moderate diaphoresis on Day 1 of Duragesic dosing with treatment with 37.5µg/h (0.99 µg /k/h). He had previously been on 180 mg of morphine/day. Both events were considered probably related to Duragesic treatment by the investigator. No intervention was made. He continued on the study medication until Day 91, when it was discontinued due to a SAE, eccymosis.
- A 3 year old boy (metastatic neuroblastoma, GBR-020) had insomnia, vivid dreams, agitation and confusion on Day 3 of Duragesic dosing with treatment with 25µg/h (1.47 µg /k/h). No rescue medication was given nor were other interventions made. He recovered from these AE and continued on study drug until his death on study Day 24.

In the published article based on study FEN-GBR-14, the investigators reported that symptoms consistent with withdrawal, e.g. diaphoresis, diarrhea, abdominal discomfort, stuffy nose and depression were detected in three pediatric patients upon conversion from oral opioids to transdermal patch. The investigators for that study noted that where recognized the symptoms responded to rescue doses of opioid or spontaneously resolved within 3 days (231.32/380). The patients referenced above, GBR-025 and GBR-020, may have been two of those patients but that cannot be definitively ascertained from the narratives and case report forms provided.

The sponsor was contacted in an attempt to determine the study ID numbers for the three patients that the FEN-GBR-14 investigators thought might have had withdrawal. The sponsor's response was "the statements made in the publication were interpretations made by the authors at the time of preparation of the manuscript and were not recorded as cases of withdrawal during the study. Listed below are those patients in our database whose constellation of reported AEs matches that discussed as representing possible withdrawal: patients GBR-1, GBR-13, and GBR-16 (fax from sponsor 4/21/2003)."

- A 15 year old (neuroblastoma, GBR-1), being treated with 50µg/h Duragesic (1.47 µg /k/h), had diaphoresis and increased hunger on Day 1. On Day 2, she complained of "feeling weepy" but had no complains of pain. On Day 3, she noted diaphoresis and depression. She received 10 mg of oramorph on study day 3. By Day 5, she was feeling better according to her diaries. She continued on study drug until her death on Day (b) (6).
- A 3 year old (metastatic Wilms tumor, GBR-13), being treated with 25µg/h Duragesic (1.6 µg /k/h), had " a blocked nose" on Days 0 and 1 but no complaints of pain until Day 2. She received 2 doses of 6 mg of oramorph on study Days 1 and 2. She discontinued study drug on Day 3. By Day 5, she was feeling better according to her diaries.
- A 15 year old (Ewings sarcoma, GBR-16), being treated with 50µg/h Duragesic (1.36 µg /k/h), had " abdominal pain" on Days 0-5. She received 12 mg of Oramorph on study Days 0-3. On Day 1, she received an additional 8 mg of Oramorph. She recovered from her AE. She was discontinued from the trial once

she ran out of diary forms without notifying the investigator, on Day 45. However, she continued to use commercially available Duragesic.

Opioid toxicity

Respiratory Insufficiency

While respiratory depression is a known serious risk of Duragesic use, in this group of patients with terminal disease, in the majority of cases it is not clear that there is a correlation between study drug use and the adverse event of respiratory insufficiency.

- A 14 year old (ALL) had bradypnea described as a SAE beginning on day 23, within 3 days of end of therapy. On the same day, this subject was reported to have dyspnea, decreased responsiveness and cardiac failure. Death occurred on study Day (b) (6) While use of study drug may have been a factor in his respiratory sy oms, it seems more likely that he had reached the terminal phase of his illness.
- A 5 year old boy (A30093, metastastic neuroblastoma) using a 25 µg/h patch (1.563 µg /kg/hr) died on Da (b) (6) of therapy. On the same day, this subject was reported to have gastrointestin bleeding, thrombocytopenia, leukocytosis, cardiac and terminal respiratory arrest. While use of study drug may have been a factor in his respiratory symptoms, it seems more likely that he had reached the terminal phase of his illness.
- An 11 year old girl (A30313, renal cancer metastatic to lung) using a 12.5µg/h patch (0.625 µg /kg/hr) died on Da (b) (6) f disease progression. On the same day, this subject was reported to hav cardiac failure and respiratory insufficiency. While use of study drug may have been a factor in her respiratory symptoms, it seem more likely that her symptoms reflected her lung metastases.
- An 11 year old (ALL, A30097) using a 75µg/h patch (1.36 µg/kg/hr) died on study Day (b) (6) of disease progression. While use of study drug may have been a factor in his respiratory symptoms, it seems more likely that he had reached the terminal phase of his illness.
- An 11 year old male (A30531, diabetes insipidus, bladder pain) had his 12.5µg/h Duragesic patch (0.28 µg /kg/hr) temporarily removed on day 1 with subsequent recovery from AE after 2 days. His respirations went from 20/min at baseline to 13 on Day 3. With temporary cessation of the 12.5 µg/h patch, the SAE resolved. Treatment was resumed at the same dose. On Day 16, his respiratory rate was noted to be 14/min. No intervention was made at that time. His respiratory rate went from the higher end of normal at 20 breaths/minute to low normal at 13 breaths/minute, which may reflect Duragesic effect on respiration or on pain.
- A 15 year old (JRA, A30548) had respiratory insufficiency reported on 1.72µg/h, 22 days on therapy, 16 days on dose. No action was taken for this SAE, which was ongoing. She was noted to have concurrent fungal pneumonia, which was the probable reason for her respiratory difficulties.

- A 10 year old male (A30530, brain abcesses) had his Duragesic patch, 12.5µg/h, temporarily removed with subsequent recovery from AE after 4 days. This AE was probably correlated with Duragesic therapy though it did not recur with continued Duragesic use.

Agitation/Nervousness

Three pediatric patients had a dose change made due to agitation/nervousness. All three recovered from this AE after the dose change was made.

- An 18 year old (Ewing's sarcoma) had a dose reduction to 25 µg/h after having been on 100 µg/h for 4 days.
- A 15 year old (ALL) had Duragesic permanently stopped after having been on 75 µg/h for 2 days.
- A 15 year old (Neuropathic pain following hip subluxation surgery) had Duragesic permanently stopped after having been on 12.5 µg/h for 63 days.

Somnolence

Seventeen of the 23 reports of somnolence occurred in the first 15 days of treatment. The majority of the patients experiencing this AE recovered without intervention. Five pediatric patients, summarized below, had a dose change made due to somnolence with subsequent recovery from this AE.

- An 18 year old (Ewing's sarcoma) had a dose reduction to 50 µg/h after having been on 75 µg/h for 21 days.
- A 6 year old (A30026, neuroblastoma) had a dose reduction to 25 µg/h after having been on 37.5 µg/h for 12 days.
- A 14 year old (metastatic osteosarcoma) had Duragesic permanently stopped after having been on 12.5 µg/h for 12 days.
- A 14 year old (A30200, sickle cell disease) had a dose reduction to 200 µg/h after having been on 225 µg/h for 2 days.
- A 14 year old (A30079) who was receiving 12.5 µg/h (0.19µg/kg/hr) withdrew from the study due to this AE. He recovered after study drug was removed.

Vomiting

Most of the patients who experienced vomiting resolved without intervention. A 6-year-old (metastatic neuroblastoma) receiving 12.5µg/h was reported not to have recovered but he still completed the primary treatment phase and entered the extension period. Four pediatric patients, summarized below, had dose changes made due to vomiting.

- A 9 year old (osteosarcoma) had a dose reduction from 25 µg/h to 12.5µg/h with subsequent recovery from AE.
- A 16 year old (PNET) had his Duragesic patches, which initially totalled 550 µg/h, lowered to 300 µg/h then stopped. He withdrew from the study two days after the onset of the AE due to insufficient pain control and died subsequent to last contact.

- A 12 year old (A30536, ANLL) who experienced vomiting beginning on Day 2 in conjunction with cerebral hemorrhage, fever, loss of consciousness had her Duragesic patches stopped on Day 3, with subsequent cessation of vomiting though the other AE were unresolved. While there is a possible correlation between the study drug and her vomiting, there is no clear correlation with her other symptoms.
- A 15 year old (A30406, ALL) experienced multiple episodes of vomiting. He recovered from the first with no intervention. His treatment with Duragesic was stopped at the third episode, on Day 13. He recovered from this AE after stopping study drug so there was a probable correlation between this AE and use of study drug.

Nausea

While the majority of the pediatric patients had no change in Duragesic in response to this AE, five pediatric patients had dose changes made due to nausea.

- A 15 year old (A30094, nonmalignant chronic pain for 4 years) had her Duragesic patch, 37.5µg/h, removed with subsequent recovery from the AE.
- A 15 year old (A30406, leukemia), with concurrent AE of fever and headache, had his Duragesic patch, 25µg/h removed without subsequent recovery from AE.
- A 16 year old (PNET) had his Duragesic patches stopped. (This patient is discussed in the vomiting subsection.)
- A 15 year old (A30419, chronic pancreatitis) had a dose reduction from 50 µg/h to 12.5 µg/h with subsequent recovery from the AE.
- A 13 year old (A30455, chronic pancreatitis) had a dose reduction from 37.5 µg/h to 25 µg/h with subsequent recovery from the AE.

E. Summary of Critical Safety Findings and Limitations of Data

These trials demonstrated that that it is possible to make a safe transition from oral/parenteral administration of opiate to a transdermal formulation in an opioid-tolerant pediatric population.

There were 97 deaths in the population of 293 patients. While almost a third of the participants died, this is not unexpected in a population of pediatric patients with predominantly solid malignancies.

Neoplasm, which did not represent a treatment emergent event, was the most commonly reported SAE. Fever and pain were also commonly reported. These SAE are not unexpected in the population under study.

The overall incidence of AEs was higher among males than females (94% versus 86%). The incidence of fever, anemia and thrombocytopenia decreased with age

of the subjects, which may reflect the underlying diagnoses. Headache and abdominal pain were more common in the eldest pediatric patients, those over 12 years old. Prepubertal subjects (Tanner stage 1) patients had a higher incidence of somnolence. Pubertal subjects (Tanner 2-5) had a greater incidence of insomnia. The youngest pediatric patients, those under 6 years old, had the highest incidence of AE reported at 98.5%. It may or may not be relevant that these pediatric patients were also receiving the highest per kilo doses of Duragesic during these trials.

Upon evaluation by underlying cause of pain, Tanner scales and initial Duragesic dose, no clinically relevant differences were noted in overall adverse event incidence. There were no unexpected adverse effects. The serious and non-serious adverse effects seen in this trial reflected the adverse events seen in the original trials of Duragesic in adults with malignancies.

There were no problems specifically attributable to Duragesic except application site reactions. The incidence of this complaint declined over time but it is not clear whether that is due to patients becoming used to the patch or whether it is due to patients deciding not to continue the study.

Fever, diarrhea, abdominal pain and nausea were all more common among US subjects and among Caucasians. While Black subjects had an AE incidence of approximately 80%, all other ethnic groups had an AE incidence of greater than 90%.

The percentage of opioid naïve pediatric patients (n=8, enrolled in study INT-24) with a non-oncologic AE was equal to or less than the percentage of opioid tolerant pediatric patients with a given non-oncologic AE.

Although only two pediatric patients were specifically stated to have withdrawal syndrome, review of the data shows that at least 8 (3%) pediatric patients had symptoms consistent with opioid withdrawal.

VIII. Dosing, Regimen, and Administration Issues

Results from pooled studies

Initial Dose

Safe and effective conversion from oral/parenteral opiates to Duragesic therapy was assessed using a population of 293 patients (see Table 15). The majority of the pediatric patients (97.3%, n=285) in these studies were opioid tolerant on enrollment, less than 3% (n=8) were opioid naïve upon study entry. Most pediatric patients were initiated with either 12.5 µg/h (n=111, 38%) or 25 µg/h (n=123, 42%) of Duragesic.

The patients on USA-87 were converted to Duragesic based on their previous morphine requirement. Patients who were receiving less than the equivalent of 45mg morphine began with 12.5µg/h Duragesic. Pediatric patients who began with 25µg/h Duragesic had been receiving the equivalent of 45-134mg morphine daily. All patients on FEN-GBR-14 were to begin with 25µg/h Duragesic or more based on their previous morphine requirement. All patients on FEN-INT-24 were to begin with 12.5µg/h.

Table 15:
Dosing and titration (pooled studies)

	Statistic	Treatment period		
		Primary	Extension	Overall
Number of subjects	n	293	168	293
Dose of analgesic taken before starting Duragesic (mg/kg/day)[1,2]	n Mean (SE)	276 3.3 (0.21)	164 3.2 (0.28)	P[6]
Duration of treatment with Duragesic (days)	n Mean (SE)	293 14.4 (0.23)	168 88.1 (11.23)	293 64.9 (6.96)
Time until first titration warranted (days)	n Mean (SE)	121 5.6 (0.24)	58 45.7 (16.06)	151 24.0 (7.38)
Time until subsequent titrations warranted[3]	n Mean (SE)	55 3.82 (0.22)	38 20.93 (3.54)	94 11.83 (1.50)
Dose of Duragesic (µg/kg/h)				
Overall	n Mean (SE)	290 1.19 (0.06)	167 1.91 (0.2)	290 1.47 (0.1)
Initial Dose	n Mean (SE)	290 0.96 (0.04)	167 1.56 (0.15)	P[6]
Final dose[4]	n Mean (SE)	290 1.4 (0.09)	167 2.47 (0.32)	290 2.00(0.2)
Dose of total opioid[1,5] (mg/kg/day)				
Overall	n Mean (SE)	290 4.89 (0.26)	167 7.44 (0.74)	290 5.81 (0.37)
Initial dose	n Mean (SE)	290 3.95 (0.185)	167 6.14 (0.56)	P[6]
Final dose[4]	n Mean (SE)	290 5.6 (0.36)	167 9.32 (1.19)	290 7. 6 (0.73)
Ratio of Duragesic to total opioid				
Overall	n Mean (SE)	293 0.91 (0.01)	168 0.94 (0.01)	293 0.92 (0.01)
Initial dose	n Mean (SE)	293 0.90 (0.01)	168 0.95 (0.01)	P[6]
Final dose[4]	n Mean (SE)	293 0.93 (0.01)	168 0.96 (0.01)	293 0.96 (0.01)

[1]Reported as its oral ME
[2]Computed for subjects who had a dose greater than 0 within 24 hours of starting Duragesic

[3]Relative to the day of the first titration in that period
[4]Defined as the last dose greater than 0 during that period
[5]Represents the sum of the total Duragesic dose plus rescue medications (FEN-USA-87 and the primary treatment period of FEN-INT-24) or only the total daily Duragesic dose (FEN-GBR-14 and the extension treatment period of FEN-INT-24)
P=identical to primary period
(ISS update Table 7:2)

Duration of therapy

The mean duration of Duragesic therapy was 65 days. In the primary treatment period, 41% (n=121) of the participants required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first dose titration during the initial treatment period, 55 (45%) required subsequent dose titration with an average time to subsequent titration of 3.8 days. As previously discussed in the Integrated Review of Safety, there were instances of temporary or permanent cessation of Duragesic usage due to SAE. There were no instances where patients who resumed Duragesic therapy resumed on dose that was lower than their initial dose.

Dose during extension period

Similar to the primary treatment period, most pediatric patients entered the extension period (n=168) receiving 12.5 µg/h (n=60, 36%) or 25 µg/h (n=72, 43%) of Duragesic. The 168 patients who entered the extension period had a mean Duragesic therapy duration of 88 days. In the extension period, 39% (n=66) of the participants required dose titration with a mean of 46 days until the first dose titration was warranted. Of the 66 patients who received dose titration during the extension period, 38 (58%) required subsequent dose titration with an average time to subsequent titration of 21 days.

Rescue medication

Duragesic represented 90% or more of the total opioid daily requirement for the subjects, with the remainder representing rescue medication used for breakthrough pain (see table 16). Rescue medication was used at least once by 89% of the subjects. The mean oral dose of rescue medication was inversely correlated with body weight. The mean oral dose of rescue medication was lowest in the subjects using the lowest strength patch at baseline and the mean dose of oral rescue was higher in persons with malignancies than in those with pain of non-malignant origin. The majority of the pediatric patients used morphine or hydromorphone as rescue medication. Fifteen pediatric patients used fentanyl, which was allowed during surgical procedures. Nine of the fifteen received a single dose of fentanyl as concomitant therapy. Five pediatric patients received 3 to 12 doses of fentanyl as rescue. One patient received 73 doses of fentanyl as rescue. Although these fifteen patients were reported as protocol violations, only one, who received a single dose, was excluded from the pharmacokinetic database.

Table 16: Rescue medication use (pooled studies)

Rescue medication	Primary treatment period n=252 (86% of 293)	Extension period n=88 (68% of 130)
Morphine	212 (84%)[a]	63 (72%)
Hydromorphone	34 (13%)	17 (19%)
Oxycodone	17 (7%)	9 (10%)
Fentanyl	15 (6%)	5 (6%)
Codeine	14 (6%)	1 (1%)
Tramadol	12 (5%)	8 (9%)
Meperidine	11 (4%)	6 (7%)
Hydrocodone	5 (2%)	3 (4%)
Methadone	5 (2%)	5 (6%)

[a]The percentages for each medication represents the percentage of rescue using pediatric patients enrolled in that period using a given compound
(data derived from Sponsor displays ISS SUB.20A/B/C, ISS update)

Titration requirements

USA-87

The mean daily dose of Duragesic during the primary treatment period was 1.4 ±0.15µg/kg/hour for pediatric patients under 6 years old, 1.23 ±0.13 µg /kg /hour for pediatric patients between 6 and 12 years old and 0.89 ±0.08 µg /kg /hour for pediatric patients over 12 years old.

Duragesic dose increased gradually during the primary treatment period for all age groups. When the pediatric patients were divided into those with malignant disease and those with non-malignant disease, the increase in average Duragesic dose was clearly driven by the former group.

Seventy-seven of the 199 patients required their first dose titration during the primary treatment period, after an average of five days.

- The five (19%) pediatric patients less than 6 years old averaged 7.6 days (median 7 days with a range from 4 to 13 days) before requiring a dose change. The median titration dose was 2.1 µg/h/kg (range 1.6-4.5 µg/h/kg). No subsequent titrations were reported for this group during the primary treatment period.
- The twenty-four (36%) pediatric patients aged 6- 12 years old averaged 6.4 days (median 4 days with a range from 2 to 13 days) before requiring a dose change. The median titration dose was 1.7 µg/h/kg (range 0.6-7.9 µg/h/kg).
- The forty-eight (47%) pediatric patients over 12 years old required a dose change after an average of 5 days (median 4 days with a range from 4 to 10 days). The median titration dose was 1.2 µg/h/kg (range 0.4-4.3 µg/h/kg).

The average time until subsequent titration was needed for patients between the ages of 6 and 16 was 3.8 days, with a median dose adjustment of 50 µg/h (range 25-200 µg/h) during the primary treatment period.

Evaluation of the 130 pediatric patients who entered the extension period (after 15 days of primary treatment) revealed that 36 pediatric patients needed further titration. The five pediatric patients who were age 6 years or younger (28%) went an average of 22 days before needing a titration, the median was 12 days with a range of 3 to 56 days. The median titration dose was 3.3 µg/h/kg (range 2.7-5.8 µg/h/kg). The 17 pediatric patients who were aged 6-12 years (39%) went an average of 13 days before needing a titration, the median was 6 days with a range of 1 to 63 days. The median titration dose was 3.0 µg/h/kg (range 0.4-15.8 µg/h/kg). The 14 oldest pediatric patients (21%) went an average of 19 days before requiring a dose titration, the median was 21 days with a range of 1 to 38 days. The median titration dose was 1.7 µg/h/kg (range 0.8-5.7 µg/h/kg).

INT-24

The protocol called for all patients in this study to begin with the 12.5 µg/h patch, however one patient began with a 37.5 µg/h patch.

Seventeen pediatric patients required their first dose titration during the primary treatment period, after five days of therapy on average. The average time until subsequent titration was needed was 3 days, with a median dose adjustment of 25 µg/h during the primary treatment period.

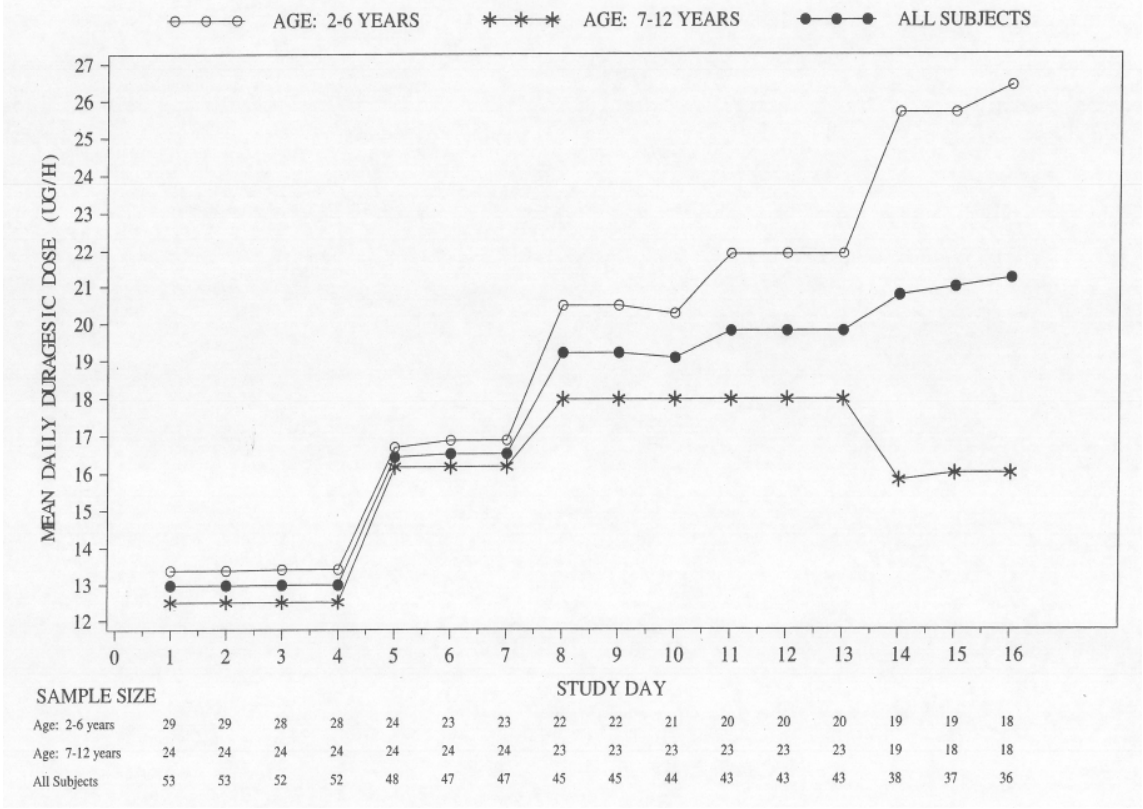
- The 8 pediatric patients (28%) under 6 years old went an average of 6 days (median 6 days with a range from 4 to 13 days) before requiring a dose change. The median titration dose was reported as 28.1 µg/h (range 25-81.3 µg/h). The median time to subsequent titration was 3 days, range 3-6 days.
- The 9 pediatric patients (38%) between 6-12 years old went an average of 5 days (median 4 days with a range from 4 to 7 days) before requiring a dose change. The median titration dose was reported as 25 µg/h (range 25-31.3 µg/h). The time to subsequent titration for all nine of these patients was 3 days.

Evaluation of the 10 pediatric patients who entered the extension period (after 15 days of primary treatment) revealed that only 4 pediatric patients needed further titration. The three pediatric patients who were age 6 years or younger went an average of 62 days before needing a titration, the median was 36 days with a range of 2 to 148 days. The one older child went 92 days before requiring a dose titration.

The increase in daily Duragesic dose over time for the primary treatment period became divergent at Day 7 when the dose for the younger pediatric patients began increasing while the requirement for the older pediatric patients reached a plateau then decreased (see graph EFF.05). This is likely attributable to disease progression in the younger age group.

During the primary treatment period, rescue dosing was higher for the pediatric patients aged 7-12 until day 8 when rescue dosing for the younger pediatric patients increased (see graph EFF.08). This increase in rescue medication use is likely attributable to disease progression in the younger age group.

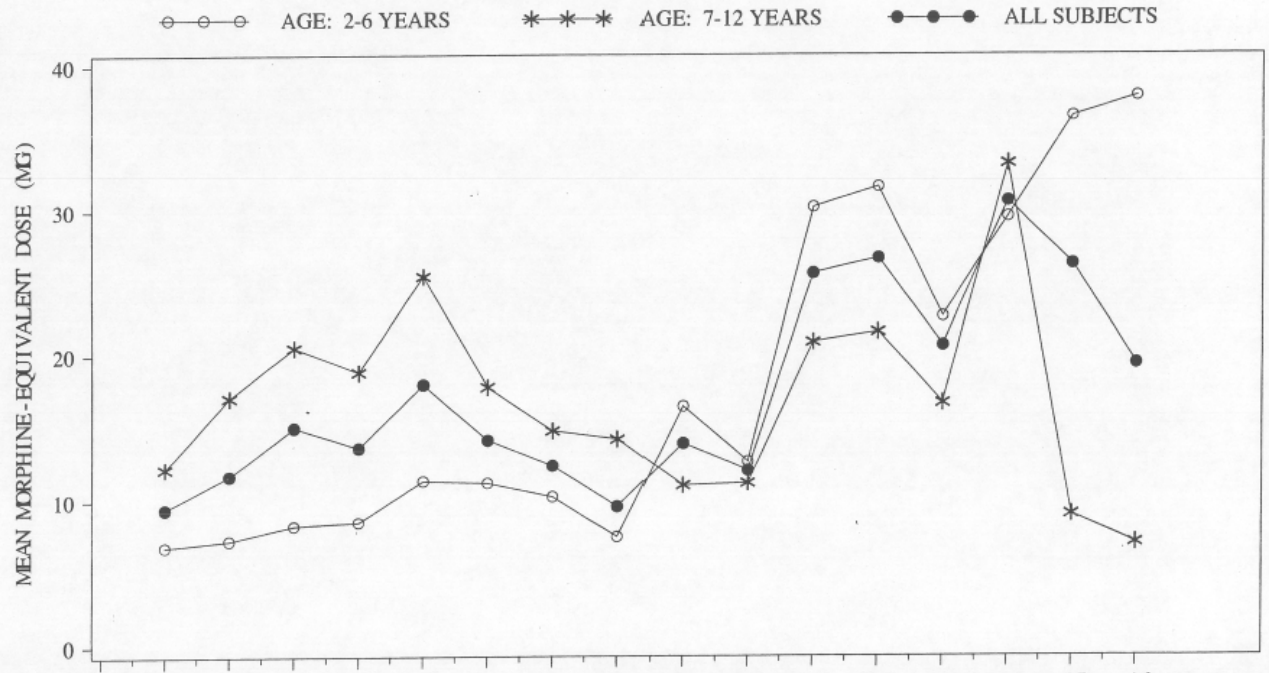
GRAPH EFF.05A AVERAGE DAILY DURAGESIC DOSAGE OVER TIME
FOR THE PRIMARY TREATMENT PERIOD--OVERALL AND BY AGE CATEGORY
POPULATION: INTENT-TO-TREAT



SAMPLE SIZE

Age: 2-6 years	29	29	28	28	24	23	23	22	22	21	20	20	20	19	19	18
Age: 7-12 years	24	24	24	24	24	24	24	23	23	23	23	23	23	19	18	18
All Subjects	53	53	52	52	48	47	47	45	45	44	43	43	43	38	37	36

GRAPH EFF.08A AVERAGE MORPHINE-EQUIVALENT DOSAGE OF RESCUE MEDICATION TAKEN OVER TIME
FOR THE PRIMARY TREATMENT PERIOD--OVERALL AND BY AGE CATEGORY
POPULATION: INTENT-TO-TREAT



SAMPLE SIZE																
Age: 2-6 years	17	18	12	11	10	11	10	11	8	9	5	5	6	7	5	2
Age: 7-12 years	16	15	15	11	9	9	9	5	7	6	5	5	3	3	3	3
All Subjects	33	33	27	22	19	20	19	16	15	15	10	10	9	10	8	5

GBR-14

The protocol called for a minimum starting dose of 25 µg/h, though initial dosing was based on the previous opioid requirements. The majority (n=34, 83%) of the subjects in this study started with a 25µg/h patch. Five subjects started with 50µg/h Duragesic. One started with 75µg/h Duragesic and one started with 150 µg/h Duragesic. The median first patch size/body weight ratio was 1.31 µg/kg/hr, range 0.37-2.38 µg/kg/hr.

Nine patients did not require dose increases during the initial fifteen day treatment phase. Of the remaining 26 patients, twelve (34%) required two dose increases. Five subjects (14%) required only one increase, while nine (38%) required three or more increases. The median last patch size/body weight ratio was 1.82 µg/kg/hr, range 0.66-8.56 µg/kg/hr.

FRA-4

This was a single dose pharmacokinetic study, using 25 µg/h Duragesic in postoperative patients. No dosing or titration information can be derived from this study.

Summary of dosage/titration findings

These trials provided adequate safety data to support the use of a 25 µg/h patch in children with a previous oral morphine equivalent requirement of 45-134 mg. The titration method, which increased Duragesic by 25µg/h for each 90mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

While in 1.5- 5 year old non-opioid patients (FEN-FRA-04), the plasma fentanyl levels were approximately twice as high as that of adult patients, in patients over 5 years old the pharmacokinetic parameters were similar to adults. These pharmacokinetics findings were taken into account in the determination of the dosing recommendations for pediatric patients.

These studies do not provide sufficient information to adequately assess the proper (b) (4).

Concomitant Medications

The entire population was evaluated for the use of concomitant medications, n=293. The majority of the patients were taking at least one other medication while on study-99.5%. The sponsor reports no clinical evidence of drug-drug interaction between Duragesic and concomitant medications.

Antiemetics

The 171 subjects who received antiemetics experienced a higher overall incidence of adverse events than the 122 subjects who did not (95% vs. 85 %). The major category of AE affected was gastrointestinal system disorders (65% vs. 52%) such as nausea, vomiting, abdominal pain. The pediatric patients using antiemetics were also more likely to have red blood cell disorders (22% vs. 10 %) and/or white blood cell and reticuloendothelial disorders (18% vs 6%).

CNS Sedatives

The 140 subjects who received CNS Sedatives experienced a higher overall incidence of adverse events than the 153 subjects who did not (96% vs. 86 %). The major category of AE affected was gastrointestinal system disorders (71% vs. 48%) such as nausea, vomiting. A disparity was also seen in general body as a whole disorders (57% vs. 48%). Convulsions (6%) and tremor (4%) were only seen in those pediatric patients receiving CNS sedatives, though the incidence of Central and peripheral nervous system disorders was also higher over all (35% vs. 24%). Respiratory disorders were higher in the group of pediatric patients receiving CNS sedatives, (39% vs. 19%). In the subcategory respiratory depression the incidence was almost equal (2% vs. 3%) and in the subcategory respiratory insufficiency, the incidence was slightly higher in the group that was not using CNS sedatives (1% vs. 2%). Pediatric patients using concomitant CNS sedatives had a higher incidence of skin and appendages disorders (38% vs. 22%), and psychiatric disorders (35% vs. 16%) with increased incidence of both somnolence (11% vs. 4%) and agitation (8% vs. 1%). Urinary tract disorders (26% vs. 9%) were more frequent in this group as were vision disorders (13% vs. 3%), Cardiovascular disorders (12% vs. 7%), musculoskeletal (10% vs. 5%), application site disorders (12% vs. 1%), and liver and biliary system disorders (7% vs. 3%). Both red blood cell disorders (14% vs. 19%) and white cell and RES disorders (9% vs. 17%) were less frequent.

Chemotherapy

The 95 subjects who received chemotherapy experienced a higher overall incidence of adverse events than the 198 subjects who did not (96% vs. 88 %). Again the major area affected is gastrointestinal system disorders (64% vs. 57%) with differences in vomiting, nausea and abdominal pain. As might be expected, body as a whole disorders, (59% vs. 49 %), resistance mechanism disorders (30% vs. 19%), platelet/bleeding and clotting disorders (23% vs. 17%), red blood cell disorders (23% vs. 14%), and white cell and RES disorders (23% vs. 9%) were all more common in this population. Skin and appendages disorders (22% vs. 31%), cardiovascular disorders (6% vs. 11%) and psychiatric disorders (18% vs. 28%) were all less common.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Both male and female patients were adequately represented in the study populations. When analyzed by gender approximately equal numbers of boys and girls had adverse events (94% vs. 86%). In most cases the incidence rates for a given AE were approximately equal. However there were a few exceptions, although the nature of thtese differences does not have apparent clinical significance.

Boys had a greater incidence of, dyspnea (6% vs. 3 %), somnolence (9% vs. 4%), insomnia (7% vs. 4%), bacterial infection (6% vs. 3%), and sepsis (5% vs. 2%).

Girls had a greater incidence of peripheral edema (8% vs. 3%), headache (19% vs. 14%), erythematous rash (6% vs. 3%), diaphoresis (5% vs. 2%), hypokalemia (6% vs 3%), urinary tract infections (7% vs. 3%), and conjunctivitis (5% vs. 2%).

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Ethnicity was only recorded for studies FEN-USA-87 and FEN-INT-24. The majority of the pediatric patients enrolled were white, hispanic or black. It should be noted that the hispanic category can comprise a mixture of pediatric patients, some of whom would be considered white, others who would be considered black. Ten pediatric patients were classified as of other ethnic groups. Those ten pediatric patients will not be included in further discussion due to small numbers per category.

While for most adverse events the incidence rates were approximately equal there were a few disparities as shown in Table 17. The majority of the patients had malignancies but the incidence was not equal across ethnic groups. The percentage of white patients with malignancies was higher than that of either black or hispanic patients (81%, 56%, 66% respectively). The higher incidence of nausea and anemia in white patients might be related to the higher proportion of patients with malignancies receiving oncologic treatment. The higher incidence of rhinitis, insomnia, anorexia and nervousness in Hispanic patients can not be explained by review of the provided materials. The reporting of only two black children with anemia seems odd in a population with 13 known sickle cell anemia patients but reporting varied by both site and investigator's determinations of whether an adverse event was treatment emergent.

Table 17:
Adverse events divided by ethnicity

	White (n=156)	Hispanic (n=45)	Black (n=41)
Number of subjects with AE	141 (90%)	42 (93%)	33 (80%)
Nausea	41 (29%)	6 (14%)	3 (9%)
Abdominal pain	19 (13%)	9 (21%)	6 (18%)
Constipation	20 (14%)	7 (17%)	3 (9%)
Diarrhea	17 (12%)	9 (21%)	5 (15%)
Hematemesis	2 (1%)	3 (7%)	2 (6%)
Fever	60 (43%)	13 (31%)	11 (33%)
Pain	18 (13%)	7 (17%)	3 (9%)
Edema	11 (8%)	1 (2%)	2 (6%)
Dyspnea	6 (4%)	5 (12%)	2 (6%)
Rhinitis	3 (2%)	6 (14%)	0
Pharyngitis	5 (4%)	3 (7%)	0
Respiratory depression	2 (1%)	3 (7%)	1 (3%)
URI	4 (3%)	3 (7%)	0

Table 17: Adverse events divided by ethnicity			
	White (n=156)	Hispanic (n=45)	Black (n=41)
Number of subjects with AE	141 (90%)	42 (93%)	33 (80%)
Pruritis	16 (11%)	6 (14%)	6 (18%)
Rash	7 (5%)	4 (10%)	2 (6%)
Diaphoresis	4 (3%)	3 (7%)	2 (6%)
Headache	27 (19%)	7 (17%)	5 (15%)
Tremor	3(2%)	1 (2%)	2 (6%)
Insomnia	4 (3%)	7 (17%)	3 (9%)
Anorexia	5 (4%)	6 (14%)	1 (3%)
Anxiety	7 (5%)	3 (7%)	0
Nervousness	1 (1%)	6 (14%)	0
Agitation	0	3 (7%)	0
Hallucinations	1 (1%)	0	2 (6%)
Sepsis	5 (4%)	1 (2%)	2 (6%)
Bacterial infection	4 (3%)	3 (7%)	4 (12%)
Anemia	33 (23%)	3 (7%)	2 (6%)
Granulocytopenia	11 (8%)	5 (12%)	0
Hypotension	3 (2%)	2 (5%)	3 (9%)
Conjunctivitis	7 (5%)	1 (2%)	1 (3%)
Application site reaction	11 (8%)	5 (12%)	1 (3%)
Cardiac failure	0	0	3 (9%)
Cardiac arrest	0	2 (5%)	1 (3%)

C. Evaluation of Pediatric Program

This application is for the addition of pediatric information to the Duragesic label.

D. Comments on Data Available or Needed in Other Populations

There was no information on hepatic or renal insufficiency requested or provided.

X. Conclusions and Recommendations

A. Conclusions

Duragesic (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic approved for use in persons over the age of 12 years.

The Sponsor has submitted this supplemental NDA in response to a pediatric written request issued by the FDA. The sponsor has met the objectives of the written request having demonstrated safe use of the product in pediatric patients as well as a safe and appropriate conversion method to Duragesic from oral and parenteral opioid therapies.

The Sponsor submitted three open-label studies of the safety and pharmacokinetics of Duragesic in the pediatric patient population. FEN-USA-87, was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years. An initial patch of 12.5 µg/h was to be placed on each subject, with replacement every 72 hours and titration as needed, based on use of rescue medication and pain assessments. FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. Additional pharmacokinetic information was obtained from FEN-FRA-4, an open-label, single dose study in eight patients between the ages of one and five years.

The majority of the pediatric patients who participated in these studies were male (n=176, 60.1 %), and lived outside of the United States of America (n=177, 60.4%). Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years (range 1-16). Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males). The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment.

These open-label trials, which did not address efficacy, demonstrated an adverse event profile in pediatric patients which is similar to the one seen in adults. Over half of the subjects (n=166, 57%) had at least one serious adverse event (SAE). Of the SAEs that could be attributed to study drug, none were unexpected for a product containing fentanyl.

The use of fentanyl in conjunction with CNS sedatives, anti-emetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events. No unexpected abnormal signal was noted on review of concomitant medications in this population so the general contraindications/warnings regarding concomitant medications will be acceptable. The known interaction with cytochrome P450 will be noted as part of general labeling for fentanyl products.

The emergence of opiate withdrawal symptoms on conversion from morphine to fentanyl has been reported in adult as well as pediatric patients. The package labeling should include specific symptoms and cautions to heighten awareness of these risks in the initial three days of Duragesic use. It should specifically be noted that these symptoms may occur in conjunction with adequate pain control. Agitation and insomnia can be associated with either withdrawal or toxicity and will have to be evaluated for each individual patient in context.

As there is not currently a 12.5µg/h patch available, patients requiring less than 45mg of morphine or equivalent opioid medications are not appropriate candidates for Duragesic therapy. The titration method, which increased Duragesic by 25µg/h for each 90mg of morphine or equivalent opioid taken as rescue medication, was well tolerated. These studies do not provide sufficient information to adequately assess the proper method of dosing an opioid naïve pediatric patient with Duragesic.

B. Recommendations

The 12.5µg/h strength and a dose of 125µg/h may be confused. It is recommended that in the development of a 12.5µg/h patch the sponsor should consider making the lowest strength patch distinctive to reduce the risk for error. One approach would be to evaluate bioequivalence of the (b) (4)

XI. Appendix

A. Adverse events in pediatric patients that did not occur in the context of a clinical trial

Age/Sex	Description of AE
3/?	Sat on patch of unknown strength. Death from respiratory failure.
3/M	Upon increasing from 25µg/h to 50µg/h, noted to have raised broken red skin at application site
6/M	Ingested some of gel from 25µg/h patch.
7/F	On 25µg/h patch noted to have shivering and trembling
8/M	On 50µg/h patch noted to have nightmares
8/M	25µg/h patch for AIDS related pain. Insomnia so patch was discontinued.
9/M	Applied 50µg/h patch prescribed for his parent. No medical intervention was given.
10/M	Application site reaction (erythematous/papular rash) while on 200µg/h
10/M	On 50µg/h patch noted to have facial swelling, shortness of breath and stridor
11/F	Pharmacologist reported that a physician ordered 25µg/h patch with instructions to cover half the patch to obtain 12.5µg/h dose. No AE noted.
11/F	On 25µg/h patch for pruritis and HIV dermatitis, had worsening of pruritis.
11/M	On 25µg/h patch for metastatic Ewing's sarcoma of leg. On day 1 of therapy pain relieved enough to allow cross-country skiing expedition. On Day 2, he was drowsy, nauseated and felt unwell. The patch was removed.
12/M	Vomiting while wearing a 25µg/h patch
12/M	Swelling from T4 dermatome upwards which resolved a few hours after removing the patch
12/F	25µg/h patch for AIDS related pain. Hallucinations experienced after patch was discontinued.
12/F	100µg/h for cancer pain. Experienced seizures followed by respiratory depression.
13/F	Chewed 50µg/h patch. No medical intervention was given.
13/M	On a 50µg/h patch for sarcoma/mucositis, on reduction to a 25µg/h patch had withdrawal symptoms
14/F	Took a hot bath while wearing patch-Application site reaction with burning and soreness
14/F	Fluid on lungs, decreased appetite, difficulty breathing, withdrawal symptoms
14/M	Applied 25µg/h patch which was not prescribed for him. No medical intervention was given.
14/M	Ingested used 25µg/h patch. No medical intervention was given.
14/M	Ingested 75µg/h patch. Complaints of pruritis and emesis.

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A. Adverse events in pediatric patients that did not occur in the context of a clinical trial (continued)

14/M	Dosage strength increased from 25µg/h to 100 over 2 months. At the last increase from 75µg/h to 100µg/h, his agitation became extreme and was accompanied by hyperactivity and insomnia. These symptoms resolved 24 hours after removal of the patch.
15/F	50 µg/h patch given for postoperative pain. Noted to have a respiratory rate of 6, hypotension and somnolence. Recovered after hospitalization in ICU and treatment with naloxone.
15/M	100 µg/h patch not effective in relieving pain
15/M	On increase from 25µg/h to 50µg/h, experienced nausea, confusion, inability to concentrate and inability to stand. Symptoms resolved once decreased to 25µg/h
15/F	Died of alveolar rhabdomyosarcoma while on 100 µg/h patch
15/F	Titrated from 25µg/h to 75µg/h then titrated to zero. Within days, anxiety, abdominal pain, chest pain radiating to arms and temporary loss of vision were reported.
15/M	While on 25µg/h patch experienced urinary retention, lethargy, vomiting and headache
Child/M	Child's grandmother was wearing a patch which came off and attached itself to her grandson. The child became ill and was taken to the hospital.
Adolescent /F	100 µg/h patch causing application site reaction with dry scaly skin under patch
Adolescent /F	100 µg/h patch causing red blotchy rash

B. Diagnoses for pediatric patients included in the ISS

Diagnosis	# (%)	USA-87	INT-24	GBR-14
Malignancy	218 (74%)	132	50	36
Hematologic	64 (29%)	48	12	4
Non-hematologic	156 (71%)	86	38	32
Non-malignancies	75 (26%)			
Burns		1	0	0
Dermatomyositis		1	0	0
Duchenne's muscular dystrophy		0	0	2
Orthopedic malformation-multiple syndromes		9	0	0
Dysuria		1	0	0
Fibromyalgia		1	0	0
Friedrich's ataxia		2	0	1
Gaucher's disease		1	0	0
GVHD		1	0	0
Hepatitis		1	0	0
JRA		5	0	0
Liver transplant		1	0	0
Metachromatic leukodystrophy		0	1	0
Microvillus inclusion disease		1	0	0
Migraines		2	0	0
Mucositis (non-oncologic)		1	0	0
Necrotizing pneumonia		1	0	0
Neurofibromatosis		2	0	0
Olmsted syndrome		0	1	0
Orthopedic injury NOS		1	0	0
Pancreatitis		11	0	0
Pleurisy		1	0	0
Postherpetic abdominal pain		1	0	0
Proteus syndrome		1	0	0
Sanfilippo's syndrome		1	0	1
Septic arthritis/osteomyelitis		1	0	0
Severe limb pain		1	0	0
Sickle Cell Disease		13	0	0
Spondylolithesis		1	0	0
Static encephalopathy		0	0	1
Subsclerosing panencephalitis		0	1	0
SLE		3	0	0
Tethered cord		1	0	0
Viral myositis		1	0	0

C. Patients who discontinued for reasons other than death or adverse events

Study / Patient #	Age/sex	reason	Study day	Dose
USA-87 A30012	11/F	Other: leaving the country	49	1.79 µg/kg/h
USA-87 A30014	14/M	Consent withdrawn	134	1.35 µg/kg/h
USA-87 A30019	11/M	Inadequate analgesia	1	1.71µg/kg/h
USA-87 A30023	15/M	Needed increased pain medicine	22	4.41µg/kg/h
USA-87 A30027	10/F	"makes pt feel bad, not effacacious"	15	0.5 µg/kg/h
USA-87 A30034	9/M	Other: patch removed	23	0.57 µg/kg/h
USA-87 A30037	7/F	Other: pain decreased	10	1.19 µg/kg/h
USA-87 A30040	13/M	Other: pain decreased	19	0.47 µg/kg/h
USA-87 A30045	6/M	Insufficient response	3	4 µg/kg/h
USA-87 A30049	12/M	Other: MD chose to wean fentanyl	58	0.33 µg/kg/h
USA-87 A30053	10/M	Non-compliant	17	0.68 µg/kg/h
USA-87 A30055	15/F	Insufficient response	7	0.72 µg/kg/h
USA-87 A30059	15/M	Insufficient response	33	0.54µg/kg/h
USA-87 A30065	9/M	Needed change in pain med	28	4.29 µg/kg/h
USA-87 A30067	13/M	Other: titrated off opioids	60	0.31 µg/kg/h
USA-87 A30076	15/M	Ineligible to continue trial	13	0.36 µg/kg/h
USA-87 A30082	10/M	Other: pain decreased	19	0.36 µg/kg/h
USA-87 A30084	7/M	Non-compliant	13	0.52 µg/kg/h
USA-87 A30086	12/M	Other: pain decreased	22	0.21 µg/kg/h
USA-87 A30087	10/M	Insufficient response	20	µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30089	2/M	Insufficient response	324	5 µg/kg/h
USA-87 A30091	9/F	Withdrew consent: felt better with morphine	55	0.806 µg/kg/h
USA-87 A30096	7/F	Insufficient response	641	14.88 µg/kg/h
USA-87 A30098	10/M	Insufficient response	6	1.85µg/kg/h
USA-87 A30099	11/F	Insufficient response	105	2.56 µg/kg/h
USA-87 A30100	7/M	Other: pain decreased	187	0.69 µg/kg/h
USA-87 A30103	1/F	Ineligible to continue trial: Age	1	3.57 µg/kg/h
USA-87 A30104	15/M	Ecchymosis	91	7.24 µg/kg/h
USA-87 A30105	13/F	Ineligible to continue trial	123	0.32 µg/kg/h
USA-87 A30106	15/F	Insufficient response	87	3.19 µg/kg/h
USA-87 A30122	5/F	Other: stopped using study drug	31	3.13 µg/kg/h
USA-87 A30134	2/M	Other: Needed increased pain medicine	22	0.96 µg/kg/h
USA-87 A30135	14/F	Other: pain decreased	32	
USA-87 A30136	9/F	Other: Needed increased pain medicine	25	0.74 µg/kg/h
USA-87 A30138	11/F	Withdrew consent: mother chose not to wait on pharmacy	25	0.83 µg/kg/h
USA-87 A30149	3/F	Other: pain decreased	19	0.89 µg/kg/h
USA-87 A30150	7/F	Insufficient response	22	4.55 µg/kg/h
USA-87 A30155	7/M	Needed patch changes q48 hours	69	2.5 µg/kg/h
USA-87 A30158	14/M	Other: obtained patch off study	250	0.71 µg/kg/h
USA-87 A30161	14/M	Withdrew consent: tired of collecting data	69	3.70 µg/kg/h
USA-87 A30162	10/M	Withdrew consent: did not want to stay in hospital	3	0.57 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30183	8/M	Other: opioid need completed	22	0.42 µg/kg/h
USA-87 A30184	13/M	Other: patches completed, care resumed by PMD	28	0.18 µg/kg/h
USA-87 A30185	15/M	Other: trial end	18	0.39 µg/kg/h
USA-87 A30189	8/M	Other: pain diminished	27	0.5µg/kg/h
USA-87 A30191	13/M	Other: pain diminished	59	0.13µg/kg/h
USA-87 A30192	14/M	Withdrew consent: mother did not want to keep records	19	1.16 µg/kg/h
USA-87 A30193	14/F	Other: patient weaned off drug	19	0.52 µg/kg/h
USA-87 A30199	13/M	Non-compliant	2	0.61 µg/kg/h
USA-87 A30200	14/M	Insufficient response	23	2.92 µg/kg/h
USA-87 A30201	2/M	Other: patient weaned off drug	61	0.89 µg/kg/h
USA-87 A30210	8/M	Withdrew consent: guardian decision	22	1.92 µg/kg/h
USA-87 A30211	9/M	Needed more frequent patch changes	19	3.79 µg/kg/h
USA-87 A30212	14/M	Withdrew consent: didn't wish to participate further	18	1.17 µg/kg/h
USA-87 A30217	2/F	Other:2 IP lost; pt dc	61	3.26µg/kg/h
USA-87 A30223	8/M	Other:MD felt pt no longer needed	13	0.42µg/kg/h
USA-87 A30224	4/F	Ineligible to continue trial	30	2.5µg/kg/h
USA-87 A30225	3/M	Other: fentanyl available off label	37	1.56µg/kg/h
USA-87 A30336	12/M	Other: fentanyl drip started	22	0.53µg/kg/h
USA-87 A30337	12/M	Other: opioid need ended	46	0.3µg/kg/h
USA-87 A30338	12/M	Other: medication available off label	21	1.72µg/kg/h
USA-87 A30339	14/F	Withdrew consent-"tired of wearing patches"	40	2.38 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30342	15/F	Ineligible to continue trial	22	0.72µg/kg/h
USA-87 A30343	15/F	Other: pain decreased	19	0.27µg/kg/h
USA-87 A30346	13/M	Other:tumor removed	120	0.33 µg/kg/h
USA-87 A30355	13/M	Ineligible to continue trial	22	1.92 µg/kg/h
USA-87 A30373	16/F	Ineligible to continue trial	1	0.25µg/kg/h
USA-87 A30384	15/F	Ineligible to continue trial	37	0.2µg/kg/h
USA-87 A30388	12/F	Ineligible to continue trial	35	1.25µg/kg/h
USA-87 A30390	11/M	Other: pain diminished	36	0.96 µg/kg/h
USA-87 A30391	9/M	Ineligible to continue trial	28	0.69 µg/kg/h
USA-87 A30392	6/F	Ineligible to continue trial	97	0.74 µg/kg/h
USA-87 A30397	5/F	Insufficient response	193	1.14 µg/kg/h
USA-87 A30403	12/M	Other: pain diminished	19	0.38 µg/kg/h
USA-87 A30409	13/F	Withdrew consent-refused to wear patches	49	1.67 µg/kg/h
USA-87 A30412	13/F	Withdrew consent-wants greater flexibility with patch management	30	0.61 µg/kg/h
USA-87 A30413	2/M	Other:ready to be tapered off opioids	21	0.96 µg/kg/h
USA-87 A30418	15/M	Ineligible to continue trial	94	0.17 µg/kg/h
USA-87 A30419	15/M	Ineligible to continue trial	76	0.33 µg/kg/h
USA-87 A30423	9/M	Ineligible to continue trial	55	0.54 µg/kg/h
USA-87 A30425	15/M	Ineligible to continue trial	49	0.27 µg/kg/h
USA-87 A30429	5/M	Other: no need for constant narcotic	22	0.5 µg/kg/h
USA-87 A30430	12/M	Other: no need for constant narcotic	18	0.28 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30455	13/M	Other: opioid taper	22	0.31 µg/kg/h
USA-87 A30456	11/M	Other: opioid taper	25	0.39 µg/kg/h
USA-87 A30481	14/M	Ineligible to continue trial	34	0.96 µg/kg/h
USA-87 A30501	2/M	Other, likely discharge	3	2.08 µg/kg/h
USA-87 A30502	15/F	Other: no longer needs patch	201	0.19 µg/kg/h
USA-87 A30513	3/F	Other: more stable using methadone rescue	37	2.78 µg/kg/h
USA-87 A30518	10/M	Other: pt switched to commercial drug	22	0.39 µg/kg/h
USA-87 A30528	12/F	Other: leaving the country	25	4.35 µg/kg/h
USA-87 A30532	14/F	Lost to followup	139	0.51µg/kg/h
USA-87 A30538	10/M	Ineligible to continue trial	19	2.84 µg/kg/h
USA-87 A30539	5/M	Ineligible to continue trial	19	0.57 µg/kg/h
USA-87 A30540	14 /F	Insufficient response	171	4.25 µg/kg/h
USA-87 A30548	15/F	Other: rheumatology-pt off patch give methadone	32	1.72 µg/kg/h
INT-24 A30003	11/F	Insufficient response	13	1.71 µg/kg/h
INT-24 A30012	5/M	Other: not happy with plaster of patch	28	0.65 µg/kg/h
INT-24 A30032	5/M	Withdrew consent: patch fell off	4	0.69 µg/kg/h
INT-24 A30035	12/F	Insufficient response	37	0.8 µg/kg/h
INT-24 A30054	5/F	Insufficient response	54	1 µg/kg/h
INT-24 A30055	7/M	Ineligible to continue trial	77	0.46 µg/kg/h
INT-24 A30056	10/M	Other: pain decreased	14	0.42 µg/kg/h
INT-24 A30057	2/F	Ineligible to continue trial	197	1.04 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

INT-24 A30058	9/M	Ineligible to continue trial	37	0.43 µg/kg/h
INT-24 A30059	9/F	Ineligible to continue trial	31	0.69 µg/kg/h
INT-24 A30077	12/M	Other: pain decreased	249	0.32 µg/kg/h
INT-24 A30092	12/M	Other: pain decreased	13	0.48 µg/kg/h
INT-24 A30095	10/M	Other:pain decreased	13	0.31 µg/kg/h
INT-24 A30158	11/F	Insufficient response	7	0.69 µg/kg/h
INT-24 A30161	4/M	Insufficient response	4	0.54 µg/kg/h
GBR-14 007	6/M	Uncontrolled pain	49	33.33µg/kg/h
GBR-14 013	3/F	Escalation of pain	2	1.6 µg/kg/h
GBR-14 016	15/F	Other: ran out of diary forms-did not contact investigator	49	0.68 µg/kg/h
GBR-14 032	13/F	Withdrew consent	28	2.31 µg/kg/h
GBR-14 033	12/M	Other:Rx changed to diamorphine by syringe driver	47	3.34 µg/kg/h
GBR-14 044	4/M	Other:Rx changed to SQ diamorphine and midazolam infusion	23	9.06 µg/kg/h
GBR-14 047	11/M	Other: pain decreased	31	0.79 µg/kg/h
GBR-14 048	10/M	Insufficient response	45	0.7 µg/kg/h
GBR-14 057	12/M	Insufficient response	1	1.96 µg/kg/h
GBR-14 062	10/M	Withdrew consent	43	0.66 µg/kg/h
GBR-14 063	12/M	Withdrew consent	17	0.51 µg/kg/h
GBR-14 075	15/M	Withdrew consent: fever	7	
GBR-14 077	6/M	Withdraw consent	14	3.56 µg/kg/h
GBR-14 101	15/M	Asymptomatic/cured	18	1.80 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

GBR-14 102	6/M	Uncontrolled pain	4	1.47µg/kg/h
GBR-14 104	16/M	Uncontrolled pain	13	4.36 µg/kg/h
GBR-14 105	6/M	Escalating pain	15	4.76 µg/kg/h

(Information derived from ISS/ISS update displays AE.12, SUB.03, and SUB .05)

D. Deaths

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
USA-87 /A30007	Extension/175µg/h	15/M	Disease progression-lymphoma	(b) (6)	0
USA-87 /A30015	Treatment/50µg/h	11/F	Disease progression-carcinoma of the cervix		0
USA-87 /A30023	Off study /last dose was 150µg/h	15/M	Respiratory insufficiency		12
USA-87 /A30026	Extension/25µg/h	6/M	Disease progression-neuroblastoma		0
USA-87 /A30028	Off study /last dose was 12.5µg/h	13/M	Progression of osteosarcoma		8
USA-87 /A30042	Extension/12.5 µg/h	14/M	Disease progression-ALL		0
USA-87 /A30045	Treatment/100µg/h	6/M	Disease progression-ALL		0
USA-87 /A30054	Off study/last dose was 25µg/h	3/F	Disease progression-ALL		6
USA-87 /A30064	Treatment/100µg/h	6/M	Disease progression-neuroblastoma		0
USA-87 /A30065	Off study/last dose was 175µg/h	9/M	Disease progression-osteosarcoma		2
USA-87 /A30070	Extension/325µg/h	10/F	Disease progression-neuroblastoma		0
USA-87 /A30085	Extension/25µg/h	13/F	Disease progression-osteosarcoma		0
USA-87 /A30093	Treatment/25µg/h	5/M	Disease progression-neuroblastoma		0
USA-87 /A30095	Treatment/25µg/h	13/M	Disease progression-ALL		0
USA-87 /A30096	Off study/last dose was 312.5µg/h	7/F	Disease progression-Wilms tumor		2
USA-87 /A30097	Extension/75µg/h	11/M	Disease progression-ALL		0
USA-87 /A30098	Off study/last dose was 25µg/h	10/M	Disease progression-Wilms tumor		7
USA-87 /A30104	Extension/275µg/h	15/M	Disease progression-nasopharyngeal carcinoma		0
USA-87 /A30122	Off study/last dose was 37.5µg/h	5/F	Disease progression-neuroblastoma		62
USA-87 /A30134	Off study/last dose was 12.5	2/M	Disease progression-hepatoblastoma		26
USA-87 /A30150	Off study/last dose was 100µg/h	7/F	Disease progression-teratoma		23
USA-87 /A30163	Treatment/25µg/h	9/F	Disease progression-neuroblastoma		0
USA-87 /A30174	Extension/12.5 µg/h	14/F	Disease progression- San Filippo's syndrome		0
USA-87 /A30180	Treatment/75µg/h	11/M	Disease progression-ANLL		15

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days) (b) (6)	Duration off study before death (days)
USA-87 /A30190	Extension/187.5µg/ h	10/F	Disease progression- extrarenal rhabdoid sarcoma		0
USA-87 /A30192	Off study/last dose was 25µg/h	14/M	Disease progression- desmoplastic small round cell tumor		143
USA-87 /A30194	Off study/last dose was 12.5µg/h	13/F	Disease progression-ANLL		36
USA-87 /A30211	Off study/last dose was 125µg/h	9/M	GI hemorrhage in child with GVHD		7
USA-87 /A30212	Off study/last dose was 75µg/h	14/M	GVHD		20
USA-87 /A30217	Off study/last dose was 75µg/h	2/F	Optic glioma		11
USA-87 /A30218	Off study/last dose was 12.5µg/h	6/M	Disease progression-ALL		25
USA-87 /A30301	Extension/25µg/h	12/M	Disease progression- glioma		0
USA-87 /A30313	Treatment/12.5µg/h	11/F	Disease progression- clear cell sarcoma of the kidney		0
USA-87 /A30321	Treatment/25µg/h	15/M	Disease progression- NHL		0
USA-87 /A30349	Treatment/12.5µg/h	3/M	Disease progression- undifferentiated carcinoma		0
USA-87 /A30355	Off study/last dose was 87.5µg/h	13/M	Disease progression- renal carcinoma		19
USA-87 /A30370	Off study/last dose was 12.5µg/h	9/F	Disease progression- neuroblastoma		13
USA-87 /A30381	Extension/12.5µg/h	12/M	Disease progression- neuroblastoma		0
USA-87 /A30389	Off study/last dose was 37.5µg/h	15/M	Disease progression- medulloblastoma		12
USA-87 /A30393	Extension/62.5µg/h	7/F	Disease progression- Ewing's sarcoma		0
USA-87 /A30394	Extension/100µg/h	2/M	Disease progression- rhabdomyosarcoma		0
USA-87 /A30396	Off study/last dose was 50µg/h	13/F	Disease progression- NHL		25
USA-87 /A30398	Extension/300µg/h	7/M	Disease progression- neuroblastoma		0
USA-87 /A30400	Extension/25µg/h	14/M	Disease progression- glioblastoma		0
USA-87 /A30408	Extension/75µg/h	10/M	Disease progression- NHL		0
USA-87 /A30448	Extension/100 µg/h	13/M	Disease progression- Ewing's sarcoma		0
USA-87 /A30466	Off study/last dose was 12.5µg/h	6/M	Disease progression- neuroblastoma		35
USA-87 /A30467	Off study/last dose was 25µg/h	14/M	Disease progression- hepatoblastoma		83

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
USA-87 /A30468	Off study/last dose was 12.5µg/h	11/M	Disease progression-osteosarcoma	(b) (6)	21
USA-87 /A30469	Off study/last dose was 25µg/h	10/M	Disease progression-medulloblastoma		40
USA-87 /A30473	Off study/last dose was 50µg/h	12/M	Disease progression-neuroblastoma		13
USA-87 /A30477	Off study/last dose was 25µg/h	8/M	Disease progression- ALL		11
USA-87 /A30481	Off study/last dose was 25µg/h	14/M	Disease progression-Ewing's sarcoma		10
USA-87 /A30496	Extension/25µg/h	10/M	Disease progression- ALL		0
USA-87 /A30501	Off study/last dose was 25µg/h	2/M	Disease progression- spinal cord rhabdoid tumor		5
USA-87 /A30503	Off study/last dose was 162.5µg/h	11/M	Disease progression-Ewing's sarcoma		4
USA-87 /A30504	Extension/<12.5µg/h	14/F	Disease progression-brainstem glioma		0
USA-87 /A30535	Extension/50µg/h	6/M	Disease progression-neuroblastoma		0
USA-87 /A30536	Treatment/25µg/h	15/F	Disease progression- ANLL		0
USA-87 /A30548	Off study/last dose was 100µg/h	15/F	Hyperkalemia, multisystem organ failure		17
INT-24 /30014	Treatment/12.5µg/h	2/F	Disease progression-retinoblastoma		0
INT-24 /30048	Treatment/12.5µg/h	3/M	Disease progression-ALL		0
INT-24 /30049	Extension/50µg/h	11/M	Disease progression-thyroid tumor		0
INT-24 /30051	Extension/75µg/h	4/M	Disease progression-rhabdomyosarcoma		0
INT-24 /30052	Extension/12.5µg/h	5/F	Disease progression-ependymoma		0
INT-24 /30053	Off study /last dose was 12.5µg/h	5/M	Disease progression-ependymoma		6
INT-24 /30078	Treatment /12.5µg/h	5/F	Disease progression-ependymoma		0
INT-24 /30085	Extension/62.5µg/h	10/F	Disease progression-glioblastoma		0
INT-24 /30091	Extension/12.5µg/h	5/M	Disease progression-neuroblastoma		0
INT-24 /30093	Treatment/25µg/h	6/F	Disease progression-neuroblastoma		0

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
INT-24 /30096	Treatment/200µg/h	3/F	Disease progression-encephalopathy	(b) (6)	0
INT-24 /30123	Off study/last dose was12.5µg/h	10/M	Disease progression-NHL		14
INT-24 /30006	Treatment/12.5µg/ h	2/M	Disease progression-neuroblastoma		0
GBR-14 /01	Extension/400µg/h	15/F	Disease progression-neuroblastoma		0
GBR-14 /08	Extension/100µg/h	18/M	Disease progression-Ewing's sarcoma		0
GBR-14 /14	Extension/150µg/h	4/F	Disease progression-Wilms' tumor		0
GBR-14 / 15	Extension/50µg/h	5/F	Disease progression-ALL		0
GBR-14 /20	Extension/75µg/h	3/M	Disease progression-neuroblastoma		0
GBR-14 /21	Extension/75µg/h	2/F	Disease progression- germ cell tumor		0
GBR-14 /23	Treatment/75µg/h	6/M	Disease progression-T cell lymphoma		0
GBR-14 /25	Extension/1400µg/ h	14/M	Disease progression-Desmoplastic small round cell tumor of pancreas		0
GBR-14 /26	Extension/100µg/h	6/M	Disease progression-Brainstem glioma		0
GBR-14 /27	Extension/50µg/h	16/F	Chest infection, failure of the left ventricle		0
GBR-14 /29	Treatment/25µg/h	16/M	Aspiration pneumonia		0
GBR-14 /33	Off study/ last dose was 175µg/h	12/M	Disease progression-glioma		2
GBR-14 /44	Off study/ last dose was 125µg/h	16/M	Disease progression-Rhabdomyosarcoma		4
GBR-14 /45	Treatment/100µg/h	7/M	Disease progression-Rhabdomyosarcoma		0
GBR-14 /46	Treatment/250µg/h	7/M	Disease progression-Rhabdomyosarcoma		0
GBR-14 /49	Treatment/75µg/h	3/F	Disease progression-Supersellar teratoma		0
GBR-14 /59	Treatment/25µg/h	17/F	Disease progression-Ovarian germ cell tumor		0
GBR-14 /60	Extension /225µg/h	18/F	Disease progression-Clear cell sarcoma		0
GBR-14 /61	Extension /75µg/h	14/M	Disease progression-Malignant Schwannoma		0
GBR-14 /69	Treatment/25µg/h	17/M	Vomiting, Cardiac Arrest, ALL		0

D. Deaths (cont.)

				(b) (6)	
GBR-14 /76	Extension /50µg/h	14/M	Disease progression-Duchenne's muscular dystrophy		0
GBR-14 /104	Off study/ last dose was 300µg/h	16/M	Disease progression-PNET		5
GBR-14 /105	Off study/ last dose was 100µg/h	6/M	Disease progression-Neuroblastoma		2
GBR-14 /108	Treatment/50µg/h	3/M	Disease progression-PNET		0
GBR-14 /113	Off study/ last dose was 75µg/h	3/M	Disease progression-Clear cell sarcoma of kidney		16

E. Serious Adverse Events (occuring in > 2% of subjects)

Total number of subjects	293
Total number of subjects with SAE	166 (56.7%)
Fever	31 (19%)
Neuroblastoma	16 (10%)
Granulocytopenia	15 (9%)
Pain	14 (8%)
Sarcoma	13 (8%)
Vomiting	11 (7%)
Dyspnea	9 (5%)
Respiratory insufficiency	9 (5%)
Anemia	8 (5%)
Sepsis	8 (5%)
Thrombocytopenia	8 (5%)
Carcinoma	7 (4%)
Lymphocytic leukemia	7 (4%)
Malignant neoplasm	7 (4%)
Respiratory depression	7 (4%)
Nausea	7 (4%)
Pancytopenia	6 (4%)
Metastases NOS	6 (4%)
Abdominal pain	5 (3%)
Cardiac failure	5 (3%)
Epistaxis	5 (3%)
Pneumonia	5 (3%)
Somnolence	5 (3%)
Cardiac arrest	5 (3%)
Infection	5 (3%)
Leukemia	4 (2%)
Pancreatitis	4 (2%)
Dehydration	4 (2%)
Malignant brain neoplasm	3 (2%)
Acute leukemia	3 (2%)
Malignant lymphoma	3 (2%)
Renal carcinoma	3 (2%)
Hypokalemia	3 (2%)
Bacterial infection	3 (2%)
Diarrhea	3 (2%)
Stupor	3 (2%)

(ISS update-display AE.13AB)

E. **Serious Adverse Events (occuring in > 2% of subjects)**
SAE that occurred in 2 or fewer patients
Neoplasm: Teratoma, astrocytoma, cervix carcinoma, malignant hepatic neoplasm, granulocytic leukemia, neoplasm NOS, non-hodgkin's lymphoma, ovarian carcinoma, malignant neoplasm of the pharnyx, retinoblastoma, malignant thyroid neoplasm

Body as a whole-general disorders: Back pain, chest pain, multiple organ failure, allergic reaction, fatigue, ischemic necrosis, edema, rigors, serum sickness, syncope, withdrawal syndrome

Respiratory system disorders: Apnea, asthma, pulmonary infiltration, sinusitis, aspiration, pharnygitis, pneumothorax, pulmonary edema, respiratory disorder

Gastrointestinal disorders: Constipation, GI hemorrhage, mucositis NOS, bowel motility disorder, pseudomembranous colitis, duodenitis, dyspepsia, enteritis, gastritis, gastroenteritis, hematemesis, intraabdominal hemorrhage, intestinal obstruction, intestinal perforation, acquired megacolon, melena, esophagitis, decreased pancreatic secretion, stomatitis

Red blood cell disorders: Hemolysis, marrow depression

White cell and RES disorders: Leucopenia, leukocytosis

Resistance mechanism disorders: herpes zoster

Metabolic and nutritional disorders: Electrolyte abnormality, lactic acidosis, enzyme abnormality, hypercalcemia, hyperglycemia, hyperkalemia, hypoglycemia, hyponatremia, increased lipase, weight decrease

Secondary terms: Fall, medication error, procedural site reaction, spinal cord compression, surgical intervention

General cardiovascular disorders: blood pressure fluctuation, hypertension, hypotension, circulatory failure

Platelet, bleeding and clotting disorders: pulmonary embolism

Heart rate and rhythm disorders: tachycardia

CNS/PNS disorders: Convulsions, encephalopathy, headache, paralysis, coma, dizziness, hypertensive encepahlopathy, hypesthesia, peripheral neuropathy, tremor, vertigo, vocal cord paralysis, nervousness, personality disorder, abnormal thinking, cerebral hemorrhage

Urinary system disorders: acute renal failure, abnormal renal function, urethral disorder, abnormal urine

E. **Serious Adverse Events, continued (occuring in > 2% of subjects)**
SAE that occurred in 2 or fewer patients
Vascular disorders: cerebrovascular disorder, intracranial hemorrhage, deep thromophlebitis, vascular disorder, varicose vein

Liver and biliary system disorders: bilirubinemia, abnormal hepatic function, hepatocelluar damage, jaundice

Skin and appendages disorders: hyperkeratosis, pruritis, rash, skin disorder, skin ulceration

Vision disorders: diplopia, eye pain, miosis, abnormal vision

Collagen disorders: graft versus host disease, auto-anitbody response

Musculoskeletal disorders: pathological fracture, hemarthrosis, myopathy

Fetal disorders: hydrocephalus

Myo-, Endo-, pericardial and valve disorders: pericarditis, pericardial effusion

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Gastrointestinal system disorders	152 (59%)	74 (56%)
Vomiting	77 (30%)	35 (26%)
Nausea	55 (22%)	23(17%)
Abdominal Pain	31 (12%)	15 (11%)
Constipation	26 (10%)	16 (12%)
Diarrhea	23 (9%)	15 (11%)
Mucositis NOS	3 (1%)	5 (4%)
Hematemesis	6 (2%)	4 (3%)
Mouth dryness	4 (2%)	3 (3%)
GI disorder NOS	0	3 (3%)
Melena	1 (1%)	3 (3%)
Pancreatitis	1 (1%)	3 (3%)
Body as a whole	120 (47%)	71 (53%)
Fever	75 (29%)	41(31%)
Pain	24 (9%)	17 (13%)
Edema	10 (4%)	8 (6%)
Peripheral edema	9 (4%)	5 (4%)
Leg pain	6 (2%)	2 (2%)
Rigors	6 (2%)	0
Abdomen enlarged	5 (2%)	2 (2%)
Allergic reaction,	5 (2%)	7 (5%)
Asthenia	5 (2%)	0
Chest pain,	5 (2%)	3 (3%)
Fatigue,	5 (2%)	1 (1%)
Abnormal lab values	5 (2%)	1 (1%)
Syncope	4 (2%)	0
Central and peripheral nervous system	64 (25%)	33 (24%)
Headache	34 (13%)	15 (11%)
Tremor	6 (2%)	1 (1%)
Convulsions	5 (2%)	6 (5%)
Dizziness	4 (2%)	2 (2%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Respiratory System disorders	53 (21%)	50 (38%)
Dyspnea	11 (4%)	7 (5%)
Coughing	7 (3%)	6 (1%)
Respiratory depression	5 (2%)	2 (2%)
Respiratory disorder	5 (2%)	0
Pharyngitis	3 (1%)	7 (5%)
Pneumonia	2 (1%)	10 (8%)
Rhinitis	4 (2%)	7 (5%)
URI	3 (1%)	6(5%)
Respiratory insufficiency	1 (1%)	4 (3%)
Bronchitis	1 (1%)	3 (3%)
Sinusitis	3 (1%)	3 (3%)
Skin and appendages disorders	71 (28%)	29 (22%)
Pruritis	32 (13%)	11 (8%)
Rash NOS	15 (6%)	4(3%)
Diaphoresis	10 (4%)	2 (2%)
Erythematous rash	8 (3%)	5 (4%)
Skin ulceration	5 (2%)	2 (1%)
Skin discoloration	2 (1%)	3 (3%)
Psychiatric disorders	54 (21%)	39 (29%)
Somnolence	16 (6%)	6 (5%)
Insomnia	11 (4%)	11 (8%)
Agitation	8 (3%)	7 (6%)
Anorexia	7 (3%)	8 (5%)
Anxiety	7 (3%)	5 (4%)
Depression	5 (2%)	0
Hallucinations	4 (2%)	2 (2%)
Nervousness	2 (1%)	4 (3%)
Confusion	1 (1%)	2 (2%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Resistance mechanisms disorders	39 (15%)	42 (32%)
Infection	8 (3%)	12 (9%)
Bacterial infection	8 (3%)	6 (5%)
Sepsis	8 (3%)	5 (4%)
Moniliasis	7 (3%)	6 (5%)
Viral infection	2 (1%)	6 (5%)
Abcess	1 (1%)	4 (3%)
Herpes Simplex	1 (1%)	4 (3%)
Otitis media	1 (1%)	5 (4%)
Platelet, bleeding & clotting disorders	39 (15%)	24 (11%)
Thrombocytopenia	22 (9%)	14 (11%)
Epistaxis	10 (4%)	10 (8%)
Purpura	4 (2%)	1 (1%)
Metabolic and nutritional disorders	37 (15%)	28 (21%)
Hypokalemia	10 (4%)	6 (5%)
Hyperglycemia	5 (2%)	0
Hypocalcemia	5 (2%)	0
Hypomagnesemia	5 (2%)	6 (5%)
Acidosis	4 (2%)	1
Fluid overload	4 (2%)	4 (3%)
Dehydration	3 (1%)	5 (4%)
Weight decrease	2 (1%)	6 (5%)
Increased creatinine	0	3 (3%)
Cachexia	0	2 (2%)
Red Blood Cell disorders	37 (15%)	28 (21%)
Anemia	33 (13%)	26 (20%)
Urinary system disorders	36 (14%)	22 (17%)
UTI	10 (4%)	6 (5%)
Hematuria	6 (2%)	5 (4%)
Urinary retention	6 (2%)	4 (3%)
Dysuria	5 (2%)	1 (1%)
Vision disorders		
Eye abnormality NOS	5 (2%)	0
White Blood Cell & RES disorders	25 (10%)	21(17%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Leukopenia	13 (5%)	7 (5%)
Granulocytopenia	8 (3%)	10 (8%)
Cardiovascular disorders	19 (7%)	12 (9%)
Hypertension	9 (4%)	2 (2%)
Hypotension	5 (2%)	3 (3%)
Cardiac failure	0	3 (3%)
Application Site Reactions	15 (6%)	6 (5%)
Heart rate and rhythm disorders	14 (5%)	5 (4%)
Tachycardia	11 (4%)	4 (3%)
Musculoskeletal system disorders	14 (5%)	14 (8%)
Skeletal pain	5 (2%)	4(2%)
Arthralgia	4 (2%)	5 (4%)
Liver and biliary system disorders	9 (4%)	6 (5%)
Vascular (extracardiac) disorders	7 (3%)	3 (2%)

Modification of sponsor's table 231.33/76, cross referenced with display AE.02B/C and updated with AE.02BB/CB. Percentages recalculated as percentage of persons experiencing an adverse event

[a]Adverse events are coded to body class and preferred term using the WHOART dictionary

[b]Subjects experiencing more than one adverse event within a body class/preferred term is counted once during that body class/preferred term

For the primary treatment period, adverse events emerging after start of study drug administration are included. For those subjects who did not enter the extension period, events occuring within the 3 day therapeutic reach of treatment were included.

G: Adverse events occurring in under 2% of the population during the primary treatment period

Adverse events that occurred in three patients
Gastro-Intestinal system disorders: GI hemorrhage/Oral hemorrhage

Body as a whole disorders: Back pain

Central and peripheral nervous system disorders: Speech disorder

Skin and appendages: Skin disorder

Psychiatric disorders: Paranoia

Metabolic and nutritional disorders: electrolyte abnormality, hyponatremia, hypoproteinemia

White cell and RES disorders: Decreased immunoglobulins

Musculoskeletal system disorders: myalgia

Liver and biliary system disorders: Bilirubinemia, jaundice

Urinary system disorders: abnormal renal function

Adverse events that occurred in two patients
Gastrointestinal system disorders: Dysphagia, Enteritis, Gastritis, Ileus, Sialorrhea, Ulcerative Stomatitis, Toothache, Tooth disorder

Central and peripheral nervous system disorders: hyperasthesia, hypoasthesia, neuralgia, neuropathy, paresthesia, paralysis, stupor

Respiratory system disorders: pulmonary infiltrate

Skin and appendages: skin dryness, skin exfoliation, skin reaction localized

Psychiatric disorders: nervousness

Platelet, bleeding and clotting disorders: coagulation disorder, gingival bleeding, hemorrhage

Red blood cell disorders: pancytopenia

Cardiovascular disorders: cardiac failure, heart murmur, cardiac arrest

G: Adverse events occurring in under 2% of the population during the primary treatment period

Vision disorders: mydriasis, blindness

Musculoskeletal system disorders: pathological fracture

Urinary system disorders: hemorraghic cystitis, micturition disorder, abnormal urine

Adverse events that occurred in one patient
Gastrointestinal system disorders: Anal fissure, Change in bowel habits, Bloody Diarrrhea, Duodenitis, Dyspepsia, Fecal abnormality NOS, Rectal hemorrhage, Intestinal perforation, Acquired megacolon, Esophagitis, Stomatitis, splenomegaly, abnormal hepatic function, elevated SGPT

Body as a whole disorders: allergy drug interaction, drug level increased, injury, multiple organ failure, mouth edema, genital edema, pallor, serum sickness, wound drainage, wound drainage increased, withdrawal syndrome, muscle weakness, wound dehiscence

Central and peripheral nervous system, Psychiatric disorders: ataxia, coma, abnormal CSF, dyskinesia, encephalopathy, hypertensive encephalopathy, hypertonia, hypokinesia, hyporeflexia, migraine, involuntary muscle contractions, peripheral neuropathy, ptosis, vertigo, depersonalization, abnormal dreaming, somnambulism, abnormal thinking

Respiratory system disorders: apnea, aspiration, asthma, bradypnea, decreased breath sounds, bronchospasm, hypoxia, pneumonitis, pneumothorax, pulmonary edema

Skin and appendages: alopecia, bullous eruption, contact dermatitis, eczema, skin depigmentation, urticaria, verruca

Platelet, bleeding and clotting disorders: hematoma, increased prothrombin time

Blood disorders: Abnormal WBC, hemolysis

Metabolic and nutritional disorders: alkalosis, decreased blood urea nitrogen, increased blood urea nitrogen, enzyme abnormality, hypercalcemia, hyperkalemia, generalized edema, periorbital edema

Cardiovascular disorders: circulatory failure, bradycardia

Vision disorders: conjunctival hemorrhage, diplopia, eye infection, eye pain, miosis, photophobia, strabismus

Urinary system disorders: bladder discomfort, cystitis, oliguria, urinary incontinence

H: Adverse events occurring in under 2% of the population during the extension treatment period

Adverse events that occurred in two patients
Gastrointestinal system disorders: Bowel motility disorder, intestinal obstruction

Central and peripheral nervous system disorders: coma

Metabolic and nutritional disorders: hyponatremia, hyperkalemia

Urinary system disorders: cystitis, abnormal renal function

Musculoskeletal system disorders: Skeletal pain

Vision disorders: Conjunctivitis

Adverse events that occurred in one patient
Gastrointestinal system disorders: Enteritis, flatulence, gastroenteritis, intrabdominal hemorrage, hiccup, esophagitis, oral hemorrhage, stomatitis, ulcerative stomatitis toothache/tooth disorder

Body as a whole disorders: Allergy, ascites, fatigue, hyperpyrexia, multiple organ failure, ischemic necrosis, genital edema, serum sickness, withdrawal syndrome

Resistance mechanism disorders: herpes zoster, fungal infection, genital moniliasis

Respiratory system disorders:Apnea, aspiration, atelectasis, bradypnea, decreased breath sounds, bronchospasm, hyperventilation, hypoxia, pleurisy, increased sputum

Psychiatric disorders: delirium, paranoia, paranoid reaction, abnormal thinking, personality disorder

Central and peripheral nervous system disorders: dyskinesia, encephalopathy, intracranial hypertension, hypertonia, hyporeflexia, meningitis neuralgia, neuropathy, paralysis, stupor, vocal cord paralysis, vertigo

Skin and appendages: alopecia, contact dermatitis, erythema, folliculitis, hyperkeratosis, skin disorder, localized skin reaction

Metabolic and nutritional disorders: lactic acidosis, increased blood urea nitrogen, hypoglycemia, hypophosphatemia, increased ldh, increased lipase, generalized edema

Urinary system disorders: oliguria, polyuria, pyuria, urinary incontinence, abnormal urine

H: Adverse events occurring in under 2% of the population during the extension treatment period (cont.)

Platelet, bleeding and clotting disorders: Pulmonary embolism, decreased prothrombin time

Red Blood cell disorders: hemolysis, marrow depression, pancytopenia

White Blood cell and RES disorders: agranulocytosis, leukocytosis, lymphadenopathy

Cardiovascular disorders: Cardiac arrest, cyanosis, circulatory failure /heart murmur

Musculoskeletal system disorders: arthritis, arthropathy, myopathy, pathological fracture

Collagen disorders: Rheumatoid arthritis, GVHD

Vision disorders: abnormal vision

I: Adverse events of special concern by system

The percentages given reflect the percentage of enrolled patients in a given age group

	Total n=293	2-<6 n=66	6-<12 n=100	12-<16 n=117	16-18 n=9
Gastrointestinal disorders					
Vomiting	98 (33%)	24 (36%)	31 (31%)	41 (35%)	2 (22%)
Nausea	69 (24%)	15 (23%)	26 (26%)	27(23%)	1 (11%)
Constipation	38 (13%)	11 (17%)	11(11%)	16 (14%)	0
Respiratory System disorders					
Dyspnea	17 (6%)	3 (5%)	3(3%)	10 (9%)	1(11%)
Respiratory insufficiency	5 (1%)	1 (2%)	3 (3%)	1 (1%)	0
Respiratory depression	7 (3%)	3 (5%)	3(3%)	1(1%)	0
Bradypnea	2 (1%)	0	0	2 (2%)	0
Apnea	2 (1%)	0	1 (1%)	1(1%)	0
Skin disorders					
Pruritis	39 (13%)	12 (18%)	12 (12%)	15 (13%)	0
Application site reaction	19 (6%)	3 (5%)	5 (5%)	11 (9%)	0
Diaphoresis	10 (3%)	2 (3%)	1 (1%)	7 (6%)	0
Psychiatric disorders					
Somnolence	21 (7%)	8	7 (7%)	5	1 (11%)
Agitation	13 (4%)	6	4 (4%)	2(2%)	1(11%)
Nervousness	7 (3%)	1(2%)	1 (1%)	4	1(11%)
Anxiety	12 (4%)	2(3%)	9 (9%)	1 (1%)	0
Insomnia	20 (7%)	2(3%)	7 (7%)	10(9%)	1(11%)
Delirium	1 (1%)	0	1 (1%)	0	0
Paranoid reaction/paranoia	4 (1%)	1(2%)	2 (2%)	1(1%)	0
Hallucinations	7 (3%)	1(2%)	4 (4%)	2(2%)	0
Systemic disorders					
Withdrawal syndrome	2 (1%)	0	0	2(2%)	0

The percentages represent the proportion of patients in a given group

(AE.22CB)

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/s/

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5/19/03 04:06:33 PM
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