CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	
Established Name	Fentanyl citrate sublingual tablets
(Proposed) Trade Name	ABSTRAL
Therapeutic Class	Opioid analgesic
Applicant	ProStrakan
Formulation(s)	(b) (4) sublingual
Dosing Regimen	PRN
Indication(s)	Breakthrough cancer pain
Intended Population(s)	Adult cancer patients receiving around the clock opioids with breakthrough pain

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that ABSTRAL (fentanyl sublingual tables) be approved for the indication: "the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain."

Evidence of efficacy was provided by a single adequate and well-controlled efficacy study in cancer patients with breakthrough pain, and supported by a Phase 2 trial. The evaluation of safety was based on a safety database of approximately 300 cancer patients with breakthrough pain, primarily those enrolled in a multiple-dose Phase 3 open-label trial.

As a 505(b)(2) application, these findings also rest, in part, on the Agency's previous findings of safety and efficacy for Actiq (oral transmucosal fentanyl citrate) which was approved for the same indication in 1998.

There are limitations to the safety data submitted by the Applicant, as follows.

1. Since ABSTRAL was being dosed in patients taking around-the-clock opioids for background pain, and the adverse event profile is expected to be similar for all opioids, the determination of causality of adverse events was difficult.

2. The patients enrolled in all trials were extremely ill and were receiving additional therapeutic agents for their underlying conditions that may have been associated with significant toxicities. This made it difficult to adequately assess and assign causality of the adverse events.

3. Because of the cross-over design of the double-blind study phase of the efficacy trial, the relationship of the time of the dose of study drug to the time of adverse event was not generally available. Nor was this information available for the open-label phases of the studies.

Despite these limitations, a thorough review of the safety data did not reveal any unexpected adverse events that could be attributed to the study drug. ABSTRAL appears to be associated with typical opioid-related adverse events, and the vast majority of serious adverse events and deaths appeared to be attributable to the patients' underlying disease, treatments, or complications of treatment. A relatively small proportion of patients had administration site reactions (oral adverse events) that could be attributed to the use of ABSTRAL.

ABSTRAL will be the forth oral transmucosal fentanyl product approved for the treatment of cancer breakthrough pain, joining Fentora Actiq, and Onsolis. All four product lines have some overlapping strengths. ABSTRAL is only bioequivalent to Actiq. Therefore, these products are not interchangeable on a microgram by microgram basis. As has become evident with Fentora and Actiq, medication errors with associated adverse events have already occurred. It is extremely important that this risk, along with the risks of overdose, abuse, misuse, and addiction, be mitigated by appropriate strategies.

1.2 Risk Benefit Assessment

Based on the efficacy and safety data presented by the Applicant from their Phase 3 clinical development program, as well as the known chemistry, pharmacology and toxicology profiles of this and other transmucosal fentanyl products, the benefits of ABSTRAL outweigh the risks for the intended use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

On 1 February 2010, the Applicant submitted a revised Risk Evaluation Minimization Strategy (REMS) for ABSTRAL to the Division. The original REMS and supporting documents were extensively revised and updated. Risk Management (DRISK) in The Office of Safety and Epidemiology (OSE), DDMAC, and DMETS have been consulted to review the Applicant's proposed REMS, and interactions between the Applicant and the Agency are ongoing at this time.

The three primary goals identified in the revised ABSTRAL REMS, (b) (4) are to:

1. Ensure appropriate patient selection for ABSTRAL, which includes avoiding ABSTRAL use in opioid non-tolerant patients
2. Educate prescribers, pharmacists and patients on the proper dosing, administration, storage and disposal of ABSTRAL
3. Reduce the potential for misuse, abuse and diversion of ABSTRAL

The (b) (4) program includes the following key features:

1. A Medication Guide (in conformance with 21 CFR 208.24) will be supplied with each ABSTRAL prescription and will include precautionary information regarding use and misuse of ABSTRAL.

2. A Communication Plan will be implemented to disseminate important risk and safety information about ABSTRAL to key stakeholders (prescribers, pharmacists, distributors and patients/caregivers).

3. The key Elements to Assure Safe Use (ETASU) of ABSTRAL will include the following:
    a. ABSTRAL will only be prescribed by healthcare providers who have completed relevant training regarding the use, misuse, and risks associated with ABSTRAL, and who are certified under 505-1(f)(3)(A).
    b. Pharmacies that dispense ABSTRAL will be certified under 505-1(f)(3)(B), and all dispensing pharmacists will receive education regarding the risks of ABSTRAL dispensing and appropriate use of the product.
    c. An enrolled drug distributor will only ship ABSTRAL to certified pharmacies.
    d. Prior to being given an ABSTRAL prescription, each patient must be enrolled in the (b) (4) program, with documentation of safe-use conditions under 505-1(f)(3)(D).

4. An implementation system, based on 505-1(f)(3)(B) and 505-1(f)(3)(D), will maintain a database of enrolled prescribers, pharmacies, and patients, monitor distribution and prescription data, and verify prescription eligibility by enrolled pharmacies prior to dispensing.

5. The Applicant will submit an assessment of the (b) (4) program to the Agency every 6 months for the first year following ABSTRAL launch, then annually thereafter. that will minimally include.

A more detailed description of the proposed REMS is provided in Section 7.7 (Additional Submissions / Safety Issues) below.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant requested a deferral of the Pediatric Assessment required under PREA (Section 7.6.3). As described in this section, the Applicant will need to fulfill the requirements of PREA.

Other Phase 4 Requests

There are no additional Phase 4 requests.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed indication for ABSTRAL (fentanyl citrate), an opioid analgesic, is the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

ABSTRAL sublingual tablet is an opioid analgesic intended for oral sublingual administration. ABSTRAL is formulated as a white tablet available in six strengths (100, 200, 300, 400, 600, and 800 mcg). The different strengths are distinguished by the shape of the tablet and by de-bossing of the first numeral of the strength on the tablet surface. Tablets are supplied in child-resistant, protective blister cards with peelable foil.

The proposed trade name, which has been found acceptable by DMETS, is ABSTRAL, and the established name is fentanyl sublingual tablets. This product is a new dosage form of fentanyl, an opioid first approved in 1968 for the intravenous treatment of pain.

2.2 Tables of Currently Available Treatments for Proposed Indications

Historically, the treatment of breakthrough pain in cancer patients has consisted of treatment of the pain episode with a short-acting, immediate-release (IR) oral opioid (or opioid/non-opioid combination product) consisting of approximately 15% of the patient's total baseline opioid dose. Typically, morphine, oxycodone, or hydromorphone have been used in this setting, however none of the IR oral opioids are approved for this indication.

There are currently three products approved for BTP in opioid-tolerant cancer patients, Actiq, Fentora, and Onsolis.

Actiq (oral transmucosal fentanyl citrate) was approved in November, 1998, specifically for the treatment of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain in. Actiq is a lozenge formulation of fentanyl citrate that, because of the highly lipophilic nature of fentanyl, is rapidly absorbed across the oral mucosa, thereby eliminating the high degree of first-pass metabolism that occurs with oral fentanyl. Because of its pharmacokinetic profile, Actiq provides rapid onset of action (approximately 15-30 minutes) combined with a relatively short duration of action, both of which make this product suitable for the treatment of a breakthrough pain episode.

The approval process for Actiq brought to light a situation where the need for a new therapy for cancer breakthrough pain had to be balanced with the management of the potential public risk associated with the marketing of a potent narcotic. This represented a unique circumstance where the population at greatest risk for adverse effects was not the population that would benefit from approval. Since Actiq was intended for use in the home, there was great concern about the appeal of this dosage form to children in the household. The Division was particularly concerned about the accidental or intentional ingestion of the product by children who had mistaken the lollipop formulation for candy.

An Advisory Committee meeting was held in September, 1997, at which time the committee voted that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health. Actiq was ultimately approved in 1998 under 21CFR§314.20 (Subpart H). Use of Actiq was restricted to cancer patients with BTP, and prescribing was restricted to Oncologists and Pain Medicine specialists. In addition, a Risk Management Plan was part of the approval.

Actiq has undergone a number of labeling changes since its approval. They include the addition of a statement advising diabetic patients that Actiq contains two grams of sugar per unit (June 10, 2002); statements added to label based on post-marketing experience regarding the association of Actiq with dental caries, tooth loss, and gum line erosion (September 24, 2004); formulation change to sugar-free (never marketed, September 9, 2005); conversion of patient leaflet (patient package insert) to MedGuide (September 6, 2006); and the addition of pharmacokinetic data for patients 5-15 years of age based on a study carried out in the pediatric population (February 7, 2007).

In September, 2006, Fentora (fentanyl effervescent buccal tablet) was approved for the same indication as Actiq. Also a reformulation of fentanyl, it is a buccal tablet that effervesces as it dissolves over a period of (b) (4) minutes. Its bioavailability is approximately 20-50% greater than that of Actiq.

Within a year of its approval, a Public Health Advisory was issued for Fentora. Reports of serious adverse events, including deaths in patients taking Fentora, had been reported to the Agency. The reports described prescribing to non-opioid tolerant patients, misunderstanding of dosing instructions, and inappropriate substitution of Fentora for Actiq by pharmacists and prescribers. Additionally, as a result of these reports, changes to the Package Insert and MedGuide were made in February 2008. These modifications, including changes to the Boxed Warning, strengthen the warnings regarding the use of Fentora in opioid non-tolerant patients including patients with migraines, correct dosing, and the conversion of patients from Actiq to Fentora

In July, 2009, Onsolis (fentanyl bioerodible mucoadhesive system) was approved for the same indication as Actiq and Fentora. Onsolis delivers fentanyl across the buccal

mucosa. The drug product is a flexible, flat, bilayer rectangle with rounded corners, with a mucoadhesive side containing fentanyl citrate that adheres upon contact with the moist buccal mucosa. The backing layer does not contain drug substance, thereby minimizing drug release into the oral cavity and maximizing transmucosal diffusion. The dose unit dissolves within 15 to 30 minutes. Compared to Actiq, the rate (approximately 60% greater maximum plasma concentration) and overall extent (40% greater exposure) of fentanyl absorption is greater with Onsolis.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently six approved drug products (not including generic forms) in the United States containing the fentanyl moiety. The table below summarizes the important aspects of regulatory and post-marketing experience with these products. The overall adverse event profiles for all of the products is similar (e.g., typical opioid effects of sedation, constipation, respiratory depression, etc.). The table below illustrates safety concerns that have occurred in addition to the expected events.

Table 1: Currently Marketed Fentanyl Containing Products

Trade Name/Established Name	NDA #	Approval Date	Major Labeling Changes	Pre- and Postmarketing Safety Concerns
Sublimaze® (fentanyl injection)	16-619	February 19, 1968	None	None
Duragesic® (fentanyl transdermal system)	19-813	August 7, 1990	• RiskMAP • Medguide • Use of overlay • Increased warnings regarding use in opioid naïve patients	• Leaking patches resulting in 2 recalls (2004 and 2008) • Lack of adhesion • Overdose, misuse and abuse • Use in opioid naïve patients
Actiq® (oral transmucosal fentanyl citrate)	20-747	November 4, 1998	• RiskMAP • Medguide • Warnings regarding dental caries	• Dental caries • Accidental pediatric exposures • Off-label use in opioid naïve patients • Abuse, misuse, overdose
IONSYS® (fentanyl iotophoretic transdermal system)	21-338	May 22, 2006	None	Never marketed due to safety issues regarding the device component
Fentora® (fentanyl buccal tablet)	21-947	September 25, 2006	• Increased warnings regarding mis-prescribing to opioid naïve patients and improper dosing • RiskMAP was part of original approval	• Off label use in opioid naïve patients • Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable
Onsolis® (fentanyl bioerodible mucoadhesive system)	22-266	July 16, 2009	• Increased warnings regarding mis-prescribing to opioid naïve patients and improper dosing • RiskMAP was part of original approval	• Off label use in opioid naïve patients • Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable

2.4 Important Safety Issues with Consideration to Related Drugs

All opioids have well established adverse event profiles that include sedation, nausea, vomiting, pruritis, hypotension and constipation. The most serious adverse reactions associated with all opioids include respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension and shock. Abuse, tolerance and physical dependence are other recognized risks associated with this class of drugs.

Because of the high potential of abuse and misuse of opioids, and experience with products such as Oxycontin and Methadone, the Agency now requires that REMS be part of the approval package for high potency opioids, including extended-release and transmucosal formulations.

All opioid labels have warnings regarding co-ingestion with alcohol, based on the additive effects of the two substances; however stronger warnings and/or non-approval of a drug could result from findings of significant dose dumping.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

ABSTRAL has been developed under IND 69,190.

A **Pre-IND meeting** was held with the Division on 6 August 2004 to provide feedback to the Applicant, (b) (4). At that time, the Applicant questioned whether pharmacokinetic studies and one efficacy study with existing documentation of fentanyl efficacy and references from the NDA for Actiq will provide sufficient evidence of efficacy for the BTcP indication.

The advice provided by the Division regarding the clinical development plan summarized, following:

- It will be necessary, in addition to the pharmacokinetic studies mentioned previously, to demonstrate efficacy with the sublingual formulation in one Phase 3 adequate and well controlled clinical trial.
- There should be 200-250 patients exposed to the dose that the Sponsor intends to market.
- An elderly population should be included in the clinical trials

An **End of Phase 2 meeting** was held with the Division on 21 September 2005 to provide guidance to the Applicant regarding the Phase 3 clinical development program. The advice provided by the Division regarding the clinical development plan included the following:

- The safety database should consist of at least 300 patients, of which at least 100 patients would be exposed for 3 months.

- Baseline background pain therapy should be stable for at least 2 weeks prior to study.
- The use of an open-label titration phase for the Phase 3 studies would be adequate to assess dose requirements, and therefore a dose ranging study would not be necessary.
- One adequate, well-controlled safety and efficacy trial with long-term safety data is acceptable for the BTcP indication.
- Complete oral cavity examinations should be performed in all Phase 3 protocols.
- The SPID30 should be used as a primary endpoint, and the planned secondary endpoints and statistical analysis are acceptable.

A Pre-NDA meeting was held on 22 April 2009 to advise the Applicant regarding the plans for submission of an NDA for their product. The Division provided the following responses regarding the clinical development plan that addressed questions from the Applicant's 13 March 2009 meeting package:

- For Study #002, the Applicant should provide statistics for the SPID30 for each dose, and include all patients regardless of completion status.
- A discussion of potential cases of diversion that occurred during clinical development should be included.
- Case report forms (CRFs) and narratives should be included for patients who:
  - Experienced an AE coded to addiction or overdose
  - Failed to return unused study medication (including stolen or missing medication supplies
  - Were discontinued prematurely from the study, (including lost to follow up, protocol non-compliance, investigator decision, protocol violation)
- Standard MedDRA queries on ISS AE data should be performed to assess severe cutaneous reactions and possible drug-related hepatic disorders.

2.6 Other Relevant Background Information

Although ABSTRAL is marketed in three other countries and authorized in 9 others, no additional relevant background information was provided by the Applicant.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to inspect two study sites in the United States. The selection of sites was based on the enrollment of study subjects,

protocol deviations and protocol violations. The reports of these inspections are pending at this writing. Based on preliminary communications with Dr. Susan Leibenhaut from DSI , data integrity regarding the efficacy trial did not appear to be compromised at these study sites.

3.2 Compliance with Good Clinical Practices

At this writing, inspection reports from DSI are pending.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454. There were no disclosed financial arrangements with clinical investigators that required further consideration.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

ABSTRAL (fentanyl) sublingual tablet is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral sublingual administration. It is designed to be placed on the floor of the mouth directly under the tongue immediately after removal from the blister card, and allowed to completely dissolve in the sublingual cavity. The intended absorption site of Abstral is across the oral mucosa. Therefore, tablets should not be chewed, sucked or swallowed. It is formulated as a white tablet available in six strengths, distinguishable by the shape of the tablet and by de-bossing on the tablet surface. ABSTRAL dissolves (b) (4) after application.

On 10 February 2010, a total of 15 deficiencies related to drug substance analytical methods for impurities, drug substance specifications, drug product, and labeling were identified by the CMC reviewer and communicated to the Applicant. The recommendation by CMC was that the application was approvable pending satisfactory resolution of these deficiencies and upon acceptable recommendations from the Office of Compliance. Interested readers are referred to Dr. Muthukumar Ramaswamy's review for a complete discussion of CMC issues.

4.2 Clinical Microbiology

No information relevant to the clinical microbiology of oral transmucosal fentanyl products was submitted with this application.

4.3 Preclinical Pharmacology/Toxicology

Referenced nonclinical information was bridged via comparable exposure data to the referenced product (Actiq). In addition, the safety profile of fentanyl has been previously investigated in a number of studies in various animal species as reported in the literature.

A complete review of the preclinical development of ABSTRAL has been performed by Dr. Beth Bolan, and those interested in further detail are referred to that review. The Pharmacology/Toxicology team has recommended Approval for this product.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, hydrocodone and oxymorphone.

4.4.2 Pharmacodynamics

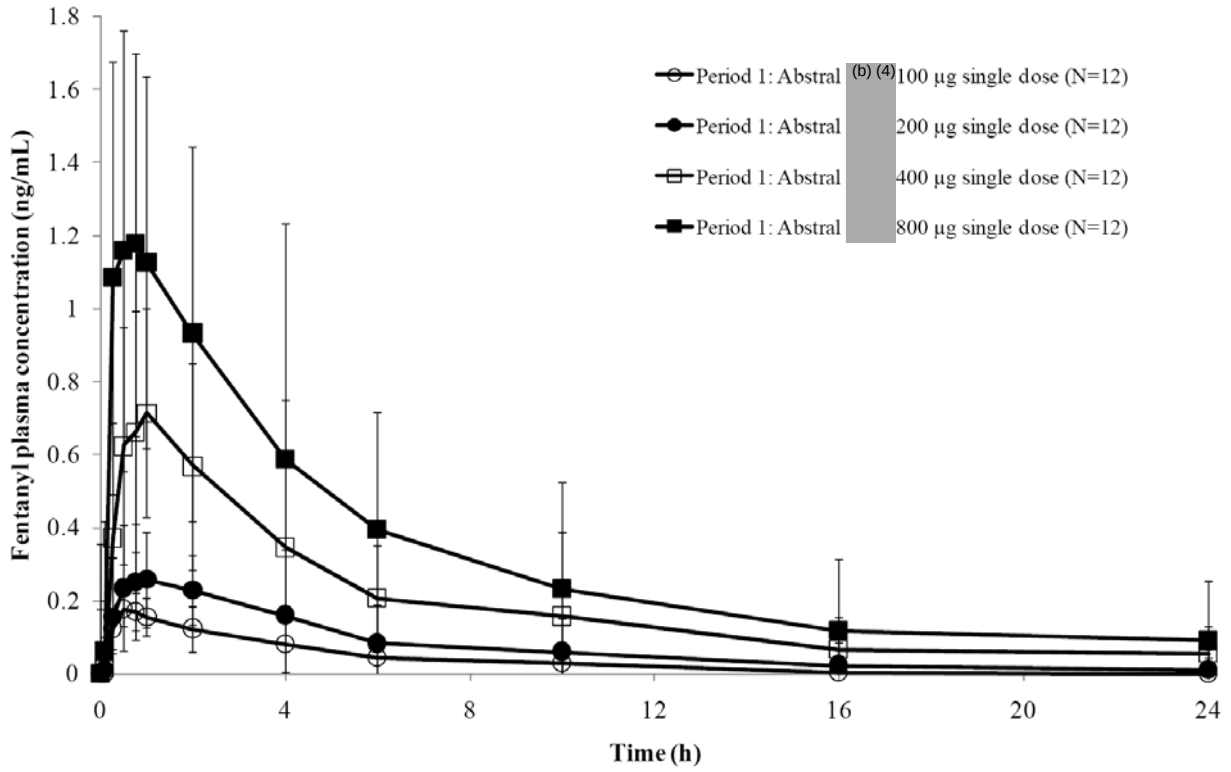
Pharmacological effects of opioid agonists are well known and include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

4.4.3 Pharmacokinetics

Absorption of fentanyl from ABSTRAL sublingual tablets is mainly through the oral mucosa, with a relative bioavailability of 54%. Dose proportionality has been observed across the 100 mcg to 800 mcg dose range Figure 1: Mean (± SD) Plasma Fentanyl Concentration versus Time after Administration of Single Doses of 100 mcg, 200 mcg, 400 mcg and 800 mcg ABSTRAL to Healthy Subjects (Figure 1), resulting in a median time to maximum plasma concentration (Tmax) across doses of 30 to 60 minutes. Pre-clinical data demonstrated that following absorption, fentanyl is initially distributed into the brain, heart, lungs, kidneys and spleen. Fentanyl is approximately 80-85% protein

bound, primarily to alpha-1-acid glycoprotein and the mean volume of distribution at steady state (Vss) was 4 L/kg. More than 90% of fentanyl is metabolized in the liver and in the intestinal mucosa to pharmacologically inactive metabolites by cytochrome P450 3A4 isoform, resulting in a median elimination half-life across doses is 5-13.5 hours. Pharmacokinetic parameters following single dose administration of ABSTRAL to healthy subjects are presented in Table 3.

Figure 1: Mean (± SD) Plasma Fentanyl Concentration versus Time after Administration of Single Doses of 100 mcg, 200 mcg, 400 mcg and 800 mcg ABSTRAL to Healthy Subjects



Source: Summary of Clinical Pharmacology Studies (Study 2246-EU-005), P. 20 of 53.

Table 2: Mean (CV%) Fentanyl Pharmacokinetic Parameters after Single-Dose Administration of 100, 200, 400 and 800 mcg Doses of ABSTRAL to Healthy Subjects (n=12 per Dose Level)

Parameter	Unit	ABSTRAL dose			
		100 mcg	200 mcg	400 mcg	800 mcg
C_{max}	(ng/mL)	0.187 (33)	0.302 (31)	0.765 (38)	1.42 (33)
T_{max} [a]	(min)	30 [19-120]	52 [16-240]	60 [30-120]	30 [15-60]
AUC_{0-inf}	(ng.h/mL)	0.974 (34)	1.92 (27)	5.49 (35)	8.95 (33)
$T_{1/2}$	(h)	5.02 (51)	6.67 (30)	13.5 (37)	10.1 (34)

a: median (range)
Source: Summary of Clinical Pharmacology Studies (Study 2246-EU-005), P. 24 of 53.

Three bioavailability/bioequivalence studies (EN3267-001, EN3267-012, and EN3267-013) were conducted by the Applicant to compare the absolute and relative bioavailability of ABSTRAL with the referenced product (Actiq). Mean plasma fentanyl concentrations versus time curves were similar (

Figure 2), and bioequivalence to the referenced product was demonstrated in two of the pivotal pharmacokinetic studies (EN3267-012, EN3267-013), while the third study failed to show bioequivalence due to incomplete consumption of Actiq.

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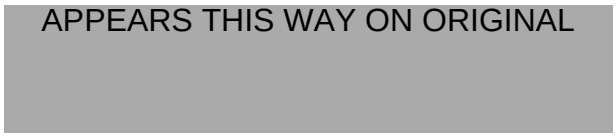
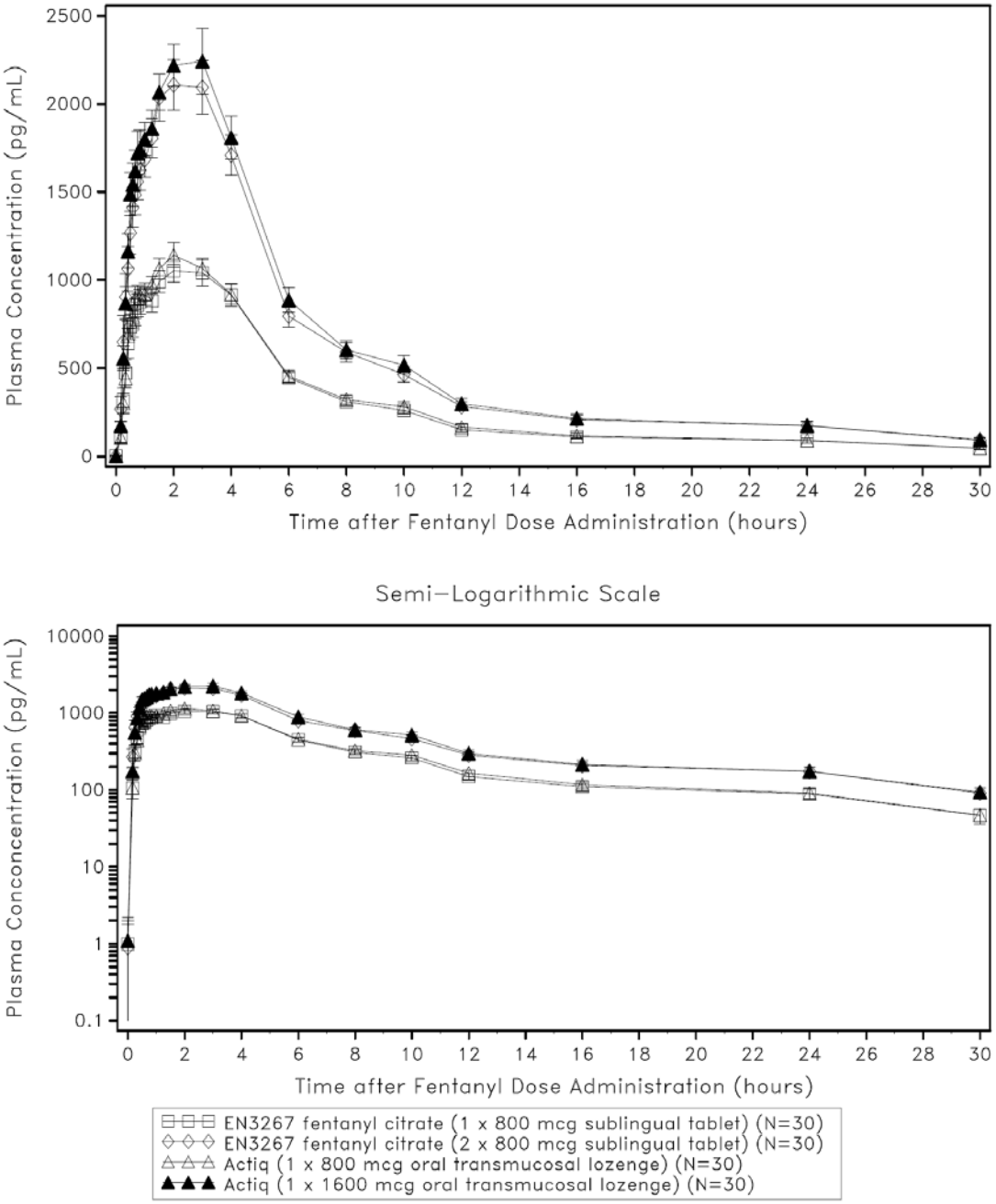


Figure 2: Mean (± SE) Plasma Concentration of Fentanyl Versus Time by Treatment – ABSTRAL (EN3267) vs Actiq



Source: EN3267-013 Clinical Study Report, P. 47 of 83.

The Office of Clinical Pharmacology felt that the NDA submission was acceptable provided that a satisfactory agreement could be reached with the Applicant regarding the Labeling for Abstral. Refer to the complete Biopharmaceutics review performed by Dr. Zhihong Li for detail regarding the clinical pharmacology aspects of ABSTRAL.

5 Sources of Clinical Data

The sources of clinical data for this review include the clinical study reports submitted by the Applicant and information from the labeling of related products.

5.1 Tables of Studies/Clinical Trials

Table 3: Summary of Clinical Studies Supporting Findings of Efficacy and Safety

Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
SuF-002	1) To evaluate pharmacodynamics of SL fentanyl with regard to PID, with primary comparison of ABSTRAL 400 mcg versus placebo in opioid tolerant patients with locally advanced or generalized cancer 2) To evaluate global assessment of treatment, need for rescue medication and dose-effect relationships upon SL administration of ABSTRAL 100, 200, and 400 mcg. To compare tolerability with regard to doses (placebo, 100, 200, and 400 mcg) and time of doses.	Randomized, multicenter, double-blind, four-period crossover study	ABSTRAL or placebo tablets; four single doses of placebo, 100, 200, or 400 mcg; SL	38 Enrolled 27 Treated 23 Completed	Three single doses (ABSTRAL 100, 200, and 400 mcg) and placebo (given in random order at consecutive pain episodes) with a washout period of at least 1 day

Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
EN3267-005	To compare the efficacy of ABSTRAL with placebo in treating BTcP in opioid-tolerant cancer patients who were using stable doses of opioid medication as measured by: 1) The SPID from Baseline to 30 min after dosing; and 2) Ratings of pain intensity, pain relief, patient global evaluation of study medication, and use of rescue medication. To evaluate the safety and tolerability of ABSTRAL in treating BTcP as measured by the occurrence of AEs and withdrawals due to AEs.	Double-blind, randomized, placebo controlled, multicenter study with an open-label titration phase followed by a non randomized, open-label, long-term extension period	ABSTRAL or placebo tablets; 100, 200, 300, 400, 600, or 800 mcg; SL	131 Enrolled Open-label Titration: 131 Treated 78 Completed Double-blind, Randomized Period a: 66 Treated 60 Completed Open-label Extension Period b: 72 Treated 25 Completed	Open-Label Titration: Titrate from 100 mcg to stable dose in 2-week period Double-Blind, Randomized Period: Receive 7 doses of stable dose and 3 matching placebo doses Open-label Extension Period: Remain on stable dose for up to 12 months
EN3267-007	To evaluate the long-term safety and effectiveness of ABSTRAL in treating BTcP episodes in opioid tolerant cancer patients who were using stable doses of opioid medication.	Multiple dose, nonrandomized, open-label, multicenter study with an open-label titration phase.	ABSTRAL; 100, 200, 300, 400, 600, or 800 mcg; SL	139 Enrolled Open-label Titration: 139 Treated 96 Completed Maintenance Period: 96 Treated 19 Completed	Open-label Titration: Titrate from 100 mcg to stable dose in 2-week period Maintenance Period: Remain on stable dose for up to 12 months

Source: Modified from ABSTRAL NDA, Tabular Listing of All Clinical Studies, P. 11-13 of 15.
Abbreviations: BTcP, breakthrough cancer pain; PID, pain intensity difference; SL, sublingual.
[a] 63 patients entered the double-blind treatment period prior to an interim analysis, 61 of whom were included in the interim analysis; 3 additional patients were engaged in the Double-blind Treatment Phase of the study at the time the interim analysis was performed and data from these patients were included in the End of-Study efficacy analysis.
[b] 72 patients entered the open-label extension period, 60 of whom first completed the double-blind treatment period and 12 of whom were enrolled under Amendment 3 and went directly from the Open-label Titration Phase to the Long term Extension Phase without entering the Doubleblind Treatment Phase.

5.2 Review Strategy

For this 505(b)(2) application, the Applicant submitted a single adequate and well-controlled efficacy study (EN3267-005). The Applicant also cited findings of efficacy for Actiq (oral transmucosal fentanyl citrate) as evidence of the efficacy of ABSTRAL.

Dr. Yan Zhou of the Division of Biometrics II reanalyzed and confirmed the Applicant's analysis of efficacy for the primary endpoint. The interested reader is referred to her review for a detailed description of the analysis and findings.

The primary electronic datasets used for the efficacy analyses were those containing data for Study EN3267-005.

Data from studies SuF-002, EN3267-005, and EN3267-007 were utilized in the integrated safety analysis. The safety review focused on adverse events, particularly deaths, serious adverse events, and morbidity related to the application site of the drug. The Integrated Summary of Safety (ISS) datasets that were used for the safety review are the following: A_AE (Adverse Events), A_ATC (Around the Clock Meds), A_DS (Disposition), A_DV (Protocol Deviations), A_EG (ECG), A_LB (Laboratory Tests), A_MH (Medical History); A_ORAL (Oral Tolerability), A_PE (Physical Exam), A_TASTE (Taste Evaluation), A_VS (Vital Signs), A_VS2 (Vital Signs).

5.3 Discussion of Individual Studies/Clinical Trials

NDA 22-510 is supported by a single adequate and well-controlled clinical trial, protocol EN3267-005.

Title
A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of EN3267 for the Treatment of Breakthrough Pain in Opioid Tolerant Cancer Patients Followed by an up to 12-Month Non-Randomized, Open-Label Extension to Assess Long-Term Safety

Objectives

Primary

1. To compare the efficacy of EN3267 with that of placebo in treating breakthrough pain episodes in opioid tolerant cancer patients who were using stable doses of opioid medication, as measured by the sum of pain intensity difference (SPID) from baseline to 30 minutes after dosing.

Secondary

2. To compare the efficacy of EN3267 with that of placebo in treating breakthrough pain episodes in opioid tolerant cancer patients, as measured by ratings of pain

intensity, pain relief, patient global evaluation of study medication, and the use of rescue medication.

3. To evaluate the safety and tolerability of EN3267 in this patient population, as measured by the occurrence of adverse events (AEs) and withdrawals due to AEs.

Study Design
Randomized, placebo-controlled, double-blind, multiple-crossover efficacy and safety trial. The study was to have been conducted in two parts:

1. A double-blind, placebo-controlled period preceded by an open-label titration and,
2. An open-label, long-term extension period

Duration
The study was to have consisted of a screening period of up to one week before enrollment (clinical laboratory tests and 12-lead ECG were to have been performed within 4 weeks of study entry), a titration period of up to two weeks, a double-blind period of up to two weeks, and a one-day follow-up. The total duration of participation in this study was to have been approximately five weeks for the open-label titration plus double-blind treatment phases of the study (EN3267-005), and up to 12 months for the open-label extension study (EN3267-007).

Sample Size
According to the original protocol, 140 subjects with cancer-related pain and frequent episodes of acute breakthrough pain superimposed on their chronic pain were to have been enrolled into the open-label titration phase of the study in order that approximately 83 subjects be enrolled in the double-blind phase of the study.

Amendment #2 (September 7, 2007), changed the enrollment to 64 subjects (approximately 75% of planned enrollment; 66 in the All Treated Patients population) entering the double-blind portion of the study as a result of recalculation of the power requirements.

Inclusion Criteria
Eligible patients were to have met all of the following criteria:

1. Males or non-pregnant females ≥ 17 years old. Female patients must be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or barrier method in conjunction with spermicide). For the purpose of this study, all females are considered to be of childbearing potential unless they are post-menopausal (at least 1 year since last menses), biologically sterile, or surgically sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation).

2. Stable cancer-related pain, defined as persistent pain of no more than moderate intensity, on average
3. A stable current regimen of oral opioids equivalent to 60-1000 mg/day of oral morphine or 50-300 mcg/hr of transdermal fentanyl, and stable dose of opioid medication for relief of breakthrough pain. "Stable" refers to an acceptable fixed dose that balances analgesia with acceptable side effects of the opioid medication (e.g., sedation, constipation, nausea/vomiting). This fixed dose must be received for at least 14 days prior to screening, and must be expected to remain unchanged for the duration of the double-blind period of the study (i.e., up to approximately 4 weeks).
4. Regularly experiencing 1-4 episodes of breakthrough pain per day, defined as a transitory flair of moderate to severe pain that occurs against a background of persistent pain controlled to moderate intensity or less by the opioid regimen. Patients must be able to identify a particular type or location of breakthrough pain as their "target pain," which will be the only pain treated with study medication throughout the study.
5. Met the criteria defined in the (b) (4) Performance Status for Grade 0, 1, or 2
6. Signed informed consent prior to enrollment in the study
7. Adjunct therapy for pain such as physical therapy, biofeedback therapy, acupuncture therapy or herbal remedies, were to remain unchanged through the titration period

Exclusion Criteria

Eligible patients were to have been excluded if any of the following applied:

1. Pregnant or lactating
2. Uncontrolled or rapidly escalating pain
3. Moderate to severe ulcerative mucositis
4. Cardiopulmonary disease that would increase the risk of administering potent opioids
5. Neurologic or psychologic disease that would compromise data collection
6. Any clinically significant condition that would, in the investigator's opinion, preclude study participation
7. Taking monoamine oxidase inhibitors (MAOIs) within previous 14 days
8. Strontium 89 therapy within previous 60 days
9. Anti-neoplastic therapy within previous 2 weeks that, in the investigator's opinion, could influence assessment of breakthrough pain
10. Any investigational drug (non-approved) within the previous 30 days or during the course of the study
11. History of hypersensitivities, allergies, or contraindications to fentanyl
12. Significant prior history of substance abuse or alcohol abuse
13. Current or planned litigation, or who are planning to acquire or are currently receiving worker's compensation or Social Security benefits, or who, in the

investigator's opinion, exhibit any evidence of secondary gain (monetary or non-monetary) associated with can correlated pain
14. Difficulty complying with the protocol, as assessed by the investigator
15. Unable to read, write or comprehend the English language questionnaires and diaries

Treatments

Titration period: All subjects were to have received open-label ABSTRAL, in escalating doses from 100-800 mcg/dose

Double-blind period: Subjects were to have received ten doses of study drug; seven doses were to have been active, and three matching placebo. Patients were to have used doses in the order specified at randomization. Placebo doses were to have been randomly distributed over the double-blind period with one placebo dose included among every three to four doses, and at least one active dose between two placebo doses.

Study Schedule of Events

Table 4: Schedule of Assessments – Open-label Titration and Double-blind Treatment Phases (EN3267-005)

		Study Phase			
		Open-label Titration[a]		Double-blind Randomized[b]	
Schedule of Assessments	Visit 1 Screening	Visit 2 Day 7	Visit 3 Day 14	Visit 4 Day 21	Visit 5 Day 28
Inclusion/Exclusion Criteria	X				
Consent Form Signed	X				
Demographic Data	X				
Medical History	X				
Physical Examination[c]	X				
Vital Signs and Body Weight	X				
Oral Cavity Examination	X	X	X	X	X
Identify Target Breakthrough Pain	X				
Clinical Laboratory Tests[d]	X				
Pregnancy Test (females of childbearing potential only)	X				X
12-lead ECG[d]	X				
Prior/Concomitant Medications	X	X	X	X	X
Patient Global Evaluation of Medication	X		X	<---------- X ---------->	
Record Breakthrough Pain Episodes in Diary[e,f]		<---------- X ---------->			
Review Eligibility for Next Phase[g]			X		
Randomization			X		
Dispense Diary and instruct on completion	X				
Dispense Study Medication	X	X	X	X	
Review Patient Diary and Re-dispense		X	X	X	X
Daily Telephone Contact[h]		<---------- X ---------->			
Pain Intensity/Pain Relief Evaluations[i]		<---------- X ---------->			
Rescue Medication Use		<---------- X ---------->			
Adverse Events		<---------- X ---------->			
Drug Accountability		X	X	X	X

See notes on next page

Source: Clinical Study Protocol (EN3267-005), Appendix 1A, P.55 of 298.
Abbreviations: ECG, electrocardiogram; QoL, quality of life.
[a] Visits every 7 (±3) days until a single dose of EN3267 can be used to treat all breakthrough pain episodes on 2 consecutive days. The open-label titration phase therefore has a minimum duration of 2 days (and a maximum duration of 14 days).

[b] Visits every 7 (±3) days until 10 breakthrough pain episodes are treated with study medication. The double-blind randomized phase therefore has a minimum duration of 4 days (and a maximum duration of 14 days).
[c] Unless conducted within 7 days of study entry.
[d] Unless conducted with 4 weeks of study entry.
[e] During open-label titration phase, the dose of EN3267 used to treat each episode of breakthrough pain is recorded.
[f] During double-blind randomized phase, the use of study medication to treat each episode of breakthrough pain is recorded.
[g] The patient must have experienced 1-4 breakthrough pain episodes/day and used a stable dose of EN3267 to treat all episodes of breakthrough pain on 2 consecutive days. (Patients may have had a day without an episode of breakthrough pain as long as at least one episode was recorded on the previous day and the subsequent day, i.e., patients must not have had 2 consecutive days without at least one episode of breakthrough pain.)
[h] To ensure proper use of study medication (including titration during the open-label titration phase, if applicable), rescue medication, completion of the diary, and to record adverse events.
[i] Recorded in diary for every breakthrough pain episode treated with study medication.

Table 5: Schedule of Study Procedures – 12-Month Extension Period (EN3267-007)

	Study Phase / Study Month / Visit Number												End-of-Study[b]
	12-Month Extension[a]												
	1	2	3	4	5	6	7	8	9	10	11	12	
Schedule of Assessments	6[c]	7	8	9	10	11	12	13	14	15	16	17	18
Review Eligibility	X												
Record Prior/Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	
Oral Cavity Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Evaluation of Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Patient Diary & Instructions for use	X												
Review Patient Diary and Re-dispense		X	X	X	X	X	X	X	X	X	X	X	
Patient Daily Diary Recordings[d]	<---------- X ---------->												
Telephone Contact[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Record Adverse Events	<---------- X ---------->												X
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X

[a] Visits every month (±2 weeks).
[b] Either at study completion (i.e., completion of Month 12) or upon discontinuation. Site personnel will contact patients 15 days after the last dose of study medication to collect information on AEs that were ongoing at the end of the study and any SAEs during this time period.
[c] Visit concurrent with end of double-blind period visit.
[d] Recorded daily in diary by patient: number of episodes of breakthrough pain, number of episodes treated with EN3267, total dose used for each episode treated with EN3267, number of episodes treated with non-study medication, and patient global evaluation of study medication.
[e] Monthly (approximately 2 weeks after monthly visit).

Source: Clinical Study Protocol (EN3267-005), Appendix 1B, P.57 of 298.

Study Conduct

Double-Blind Period with Open-Label Titration (EN3267-005)

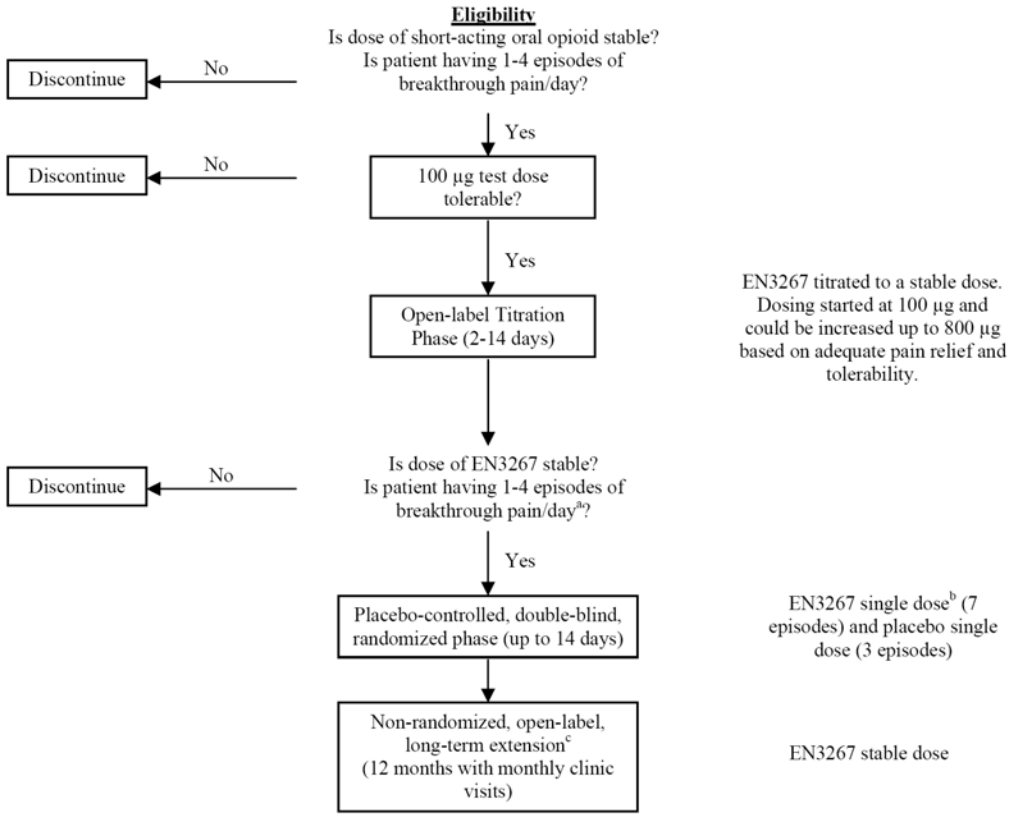
The first part of this study was to have been conducted using a double-blind, randomized, placebo-controlled design to compare the efficacy of EN3267 with placebo in the treatment of breakthrough pain in opioid tolerant cancer patients. The double-blind part was to have consisted of two phases: an open-label titration phase, during which patients were to have up to 2 weeks to determine a single effective dose of EN3267 for adequate treatment of breakthrough pain, followed by a double-blind, randomized, placebo-controlled phase of up to 2 weeks, during which 10 episodes of breakthrough pain were to be treated with study medication. At the start of the open-label titration phase, all patients were to be administered 100 mcg EN3267 for the first

episode of breakthrough pain. If pain relief was insufficient after 30 minutes, rescue medication (i.e., previously prescribed drug/dose of breakthrough medication, which was to be provided by the investigator) could be used and the EN3267 dose used for the subsequent breakthrough pain episode was to be increased to the next higher dose (200 mcg). If a patient experienced intolerable side effects after any 100 mcg dose of EN3267, he/she was to be discontinued from the study. Intolerable AEs in subsequent episodes were to result in a reduction of the EN3267 dose. Patients were to be instructed to wait at least 2 hours before treating another breakthrough pain episode with EN3267. Dosing was to continue in this manner until effective pain relief was achieved using a single dosage strength of EN3267 for all breakthrough pain episodes on 2 consecutive days. Patients were up-titrated as follows: 100 mcg to 200 mcg to 300 mcg to 400 mcg to 600 mcg to a maximum dose of 800 mcg. Patients who were not able to treat breakthrough pain episodes with a single stable EN3267 dose by the end of 2 weeks were to be discontinued from the study. After identification of a single effective EN3267 dose, eligible patients were to enter the double-blind, randomized, placebo-controlled phase. Each patient was to receive 10 doses of study medication, comprising 7 doses of EN3267 at the stable dose identified during the titration period and 3 matching placebo doses. The randomization scheme would determine the order in which each patient would receive the 10 study medication tablets. For each episode of breakthrough pain during this phase, the patient was to be instructed to use one dose of study medication in the exact order specified on the study medication packaging. If pain relief was insufficient after 30 minutes, rescue medication (previously prescribed drug/dose of breakthrough medication) could be used. Patients were to be instructed to wait at least 2 hours before treating another episode of breakthrough pain with study medication.

Open-Label Long-Term Extension (EN3267-007)

The second part of the study was to be conducted using a non-randomized, open-label design in which patients who completed the double-blind period were to use EN3267 to treat breakthrough pain episodes over a 12-month period. This extension was included to provide data on the longer term exposure to EN3267. Patients were to return to the study site monthly (±2 weeks); site personnel were to contact patients via telephone monthly, i.e. approximately 2 weeks after the monthly visits.

Figure 3: Study Flow Chart



Source: Clinical Study Protocol (EN3267-005), Figure 1, P. 17 of 298.

Removal of Subjects from Therapy or Assessment

Patients were to have been discontinued from the study for any of the following reasons, if deemed appropriate, by the Applicant or investigator:

- Entry into the study in violation of the protocol
- Protocol violation during the study
- Withdrawal of consent (reason for the withdrawal must be specified)
- Change in the condition of a patient after entering the study such that the patient either no longer meets the inclusion criteria or develops any of the exclusion criteria.
- If, in the investigator's opinion, it was not in the patient's best interest to continue (reason for the withdrawal was to have been specified)

A protocol violation was defined as a serious deviation from protocol-specified procedures that could potentially bias interpretation of efficacy analyses. Patients were to have been discontinued from the study for the following protocol violations:

- Less than 1 or more than 4 episodes of breakthrough pain per day during the open-label titration phase. Patients could have had 1 day in the open-label titration phase during which there was no breakthrough pain episodes. However, this day without breakthrough pain could not have occurred during the final 2 days of the open-label titration phase.
- Unstable oral opioid or transdermal fentanyl regimen. If changes to a patient's fixed schedule oral opioid or transdermal fentanyl regimen were clinically indicated at any time during the titration/double-blind period of the study, the patient was to have been discontinued.

When a patient was "lost to follow-up" (i.e., failed to return for study visits), a reasonable effort should have been made to contact him/her to determine a reason for the failure to return; the patient should have been identified as "lost to follow-up" in the case report form (CRF).

The date a patient discontinued and the reason for discontinuation were to have been recorded on the CRF. If a patient discontinued from the study (regardless of the cause), all end-of-study procedures should have been conducted. If, however, a patient withdrew consent, no end-of-study procedures were required except the collection of AE information. This information should have been recorded in the source document and in the CRF.

Concurrent therapy
Any concomitant therapy used while the patient was in the study was to have been recorded on the CRF, which was to include the medication name, dosage, date, time**,** and indication for use. The medical monitor was to have been notified in advance of (or as soon as possible after) any instances in which prohibited therapies are administered.

Each patient's fixed-schedule oral opioid or transdermal fentanyl regimen was to have remained unchanged from the time the patient entered the study and during the double-blind period. If changes to the patient's opioid or transdermal fentanyl regimen were clinically indicated during the open-label period of the study, the patient was to have been discontinued. Use of any short-acting opioid pain medications other than those specified in the protocol was prohibited.

The following medications and therapies were to have remained at a stable dose/regimen throughout the titration period:

- Tranquilizers
- Muscle relaxants
- Sedatives
- Antidepressants
- Anticonvulsants
- Benzodiazepines

- Physical therapy
- Biofeedback therapy
- Acupuncture therapy
- Herbal remedies

Rescue Medication
Subjects were to have been allowed their usual rescue medication (i.e., previously prescribed drug/dose of breakthrough pain medication) 30 minutes after study drug administration if adequate pain relief had not occurred. This was to have been permitted during the titration and double-blind periods of the study.

Outcome Measures
Efficacy
For each episode of target BTcP treated with study medication, subjects were to have recorded on their electronic diary (invivodata, Inc.) the dose of study medication (100, 200, 300, 400, 600, or 800 mcg) used, if any, to treat an episode of BTcP. Response information was to have been recorded using the pain scales immediately before and at 5, 10, 15, 30, and 60 minutes after taking study drug.

- Pain intensity: Subjects were to have been asked to "Please rate your pain by indicating the one number that tells how much pain you have right now." Subjects were to have rated their pain intensity on an 11-point scale ranging from 0 = no pain to 10 = pain as bad as you can imagine.
- Pain relief: Subjects were to have been asked the following questions: "How much pain relief do you have now compared to immediately prior to taking the study medication?" Subjects were to have rated their pain relief using a 5-point scale as: 0=no relief; 1=slight relief; 2=moderate relief; 3=lots of relief; and 4=complete relief.
- Global evaluation of medication: Patient's evaluation of current breakthrough medication was to have been assessed at screening. Additionally, patient evaluation of study medication was to have been assessed 60 minutes after each dose during the double-blind phase or upon rescue, and during the open-label, long-term extension period. At the end of the double-blind phase, patient satisfaction with EN3267 compared with their previous breakthrough medication was to have been assessed.
- Rescue mediation: The date, time and use of rescue medication after study drug administration were to have been recorded for each BTcP episode.

Primary Efficacy Endpoint
The primary efficacy endpoint was to have been the sum of pain intensity differences (SPID) from baseline to 30 minutes after treating BTcP episodes with study medication. Baseline for each episode is defined as the pain score recorded prior to taking study medication for that episode. The pain intensity difference (PID) at each time point was

to be the score at baseline minus the score at that time point. The mean SPID across episodes for each treatment for each patient was to be calculated prior to analysis.

Secondary Efficacy Endpoints

- PID at each time point (i.e., 10, 15, 30, and 60 minutes)
- Pain relief (PR) scores at each time point (i.e., 10, 15, 30, and 60 minutes)
- Total pain relief (TOTPAR) at 30 and 60 minutes
- SPID at 60 minutes
- Percentage of treated breakthrough pain episodes that require use of rescue medication
- Percentage of responders (defined as patients who have at least a 30% decrease in pain intensity from baseline to 30 minutes [{PID_30/baseline}*100])
- Patient global evaluation of study medication
- Use of rescue medication

Amendment#1 (November 15, 2006) added the quality of life (QOL) measures, Brief Pain Inventory (BPI), and Depression, Anxiety,and Positive Outlook Scale (DAPOS).

Safety

Safety was to have been evaluated by adverse event (AE) reporting, vital signs, and physical examination findings (including oral cavity).

Beginning with the first dose of study medication and throughout the study, AEs were to have been documented on the source document and on the appropriate page of the case report form (CRF) whether or not considered treatment-related. This was to include any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening were to have been recorded as part of the patient's medical history. The investigator was responsible for assessing the relationship of AEs to the study medication; relationship was to be classified as not related, unlikely related, probably related, or possibly related (see Section 6.2.1.2 for definitions). All AEs that were ongoing at the time of study completion were to have been followed to resolution or for 15 days after the last dose of study medication (whichever occurred first). Any serious adverse event (SAE), including death resulting from any cause, which occurred to any patient participating in this study or within 15 days following cessation of the study treatment or premature discontinuation from the study whether or not related to the investigational product, was to have been reported via facsimile or telephone within 24 hours of first being advised of the SAE. Follow-up information collected for any initial report of an SAE was to have been reported to the Applicant within 24 hours of receipt by the investigator.

AEs were to be coded using a standardized dictionary (Medical Dictionary for Regulatory Activities [MedDRA] Version 8.0). Incidence of AE analyses were to be

presented overall, by system organ class and preferred term. Severity and relationship to study medication of the incidence of AEs were also to be presented. AEs causing early withdrawal and incidence of SAEs were to be summarized. Treatment-emergent AEs (TEAEs) were to be recorded through the last study visit; ongoing AEs were to be re-evaluated and new SAEs were to be recorded up to 15 days after the last dose of study medication.

Statistical Analysis

The following patient populations were to have been used for analysis: all treated (titration and double-blind phases), intent-to-treat, and per-protocol. The definitions of these datasets follow:

- All Treated Patients (titration phase): All patients who received at least one dose of the open-label titration medication. Safety data from the open-label titration phase was to be summarized using this population.
- All Treated Patients (double-blind phase): All patients who received at least one dose of double-blind medication. Safety data in the double-blind phase was to have been summarized using this population.
- Intent-to-Treat (ITT) Population: All randomized patients who received at least one dose of double-blind study medication and provided baseline and at least one post-baseline pain intensity score. All efficacy analyses were to have been performed using this population.
- Per-protocol Population: All ITT patients with evaluable episodes that were compliant with the protocol. Unevaluable episodes were to be excluded for reasons such as: pain treated not target breakthrough pain, change to current pain medication, incomplete episodes, etc.

The primary efficacy analysis was to be based on the ITT population using the primary endpoint. The primary efficacy endpoint, i.e., SPID at 30 minutes after dosing, was to be analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment, center, sequence, and random effect for patient. The OM option was to be used in estimating the least squares means for treatment groups to weight each center according to the number of patients treated in that center. Least squares means, p-values and 95% confidence intervals of the treatment difference were to be calculated.

The supportive analyses were to include analyses of secondary endpoints based on the ITT population and all endpoints on the per protocol population. All secondary parameters, including PID and PR scores at all time points, SPID at 60 minutes after dosing, TOTPAR at 30 and 60 minutes after dosing, were to be analyzed in the same manner as the primary endpoint.

The percentage of treated breakthrough pain episodes that required the use of rescue medication between the two treatment groups were to be summarized. The episodes

with rescue medication were to be analyzed using a logistic regression with repeated measure. Odds ratios and their 95% confidence intervals were to be calculated.

The percentage of responders between the two treatment groups were to be summarized. Responders were to be analyzed using a logistic regression with repeated measure. Odds ratios and their 95% confidence intervals were to be calculated.

Patient global evaluation of medication between the two treatment groups were to be analyzed in the same manner as the primary endpoint.

Unless otherwise specified, all statistical tests were to have been two-sided with a significance level of $\alpha = 0.05$.

No adjustments were described or made for multiplicity of secondary endpoints.

Safety analysis
Safety data in the open-label titration phase were to be summarized using the All Treated Patients (titration phase) population. Safety data in the double-blind phase were to be summarized using the All Treated Patient (double-blind) population. Data were also to be summarized for both phases combined. TEAEs and SAEs were to be recorded up to 15 days after the last dose of study medication and summarized in tables, and all AEs were to be presented in the data listings.

Summary of Protocol Amendments

Amendment #1 (November 15, 2006):

- Administrative changes
- Include the quality of life (QOL) measures Brief Pain Inventory (BPI) and Depression, Anxiety, and Positive Outlook Scale (DAPOS)
- Include administration of a test dose of study medication during the screening visit and additional procedures (observation and vital signs)
- Specify criteria used for rating ulcerative mucositis
- Include use of a patient Dosing Instruction Card
- Add clarity to the prohibited and stable-use concomitant medications and therapies
- Clarify the scheduling of the end of double-blind period visit including the use of rescue medication for delayed visits
- Include pregnancy test for women of childbearing potential at the end-of-study evaluations
- Include All Treated Patients (Entire Study) and All Treated Patients (Long-Term Extension Phase) populations for analysis of safety data
- Add clarity to handling of missing data for discontinued patients
- Broaden the definition of small centers for data analysis

Amendment #2 (September 7, 2007):

- Administrative changes
- Removal of life expectancy criterion
- Removal of the requirement for an in-home caregiver
- Addition of interim analysis plan

Amendment #3 (December 18, 2007):

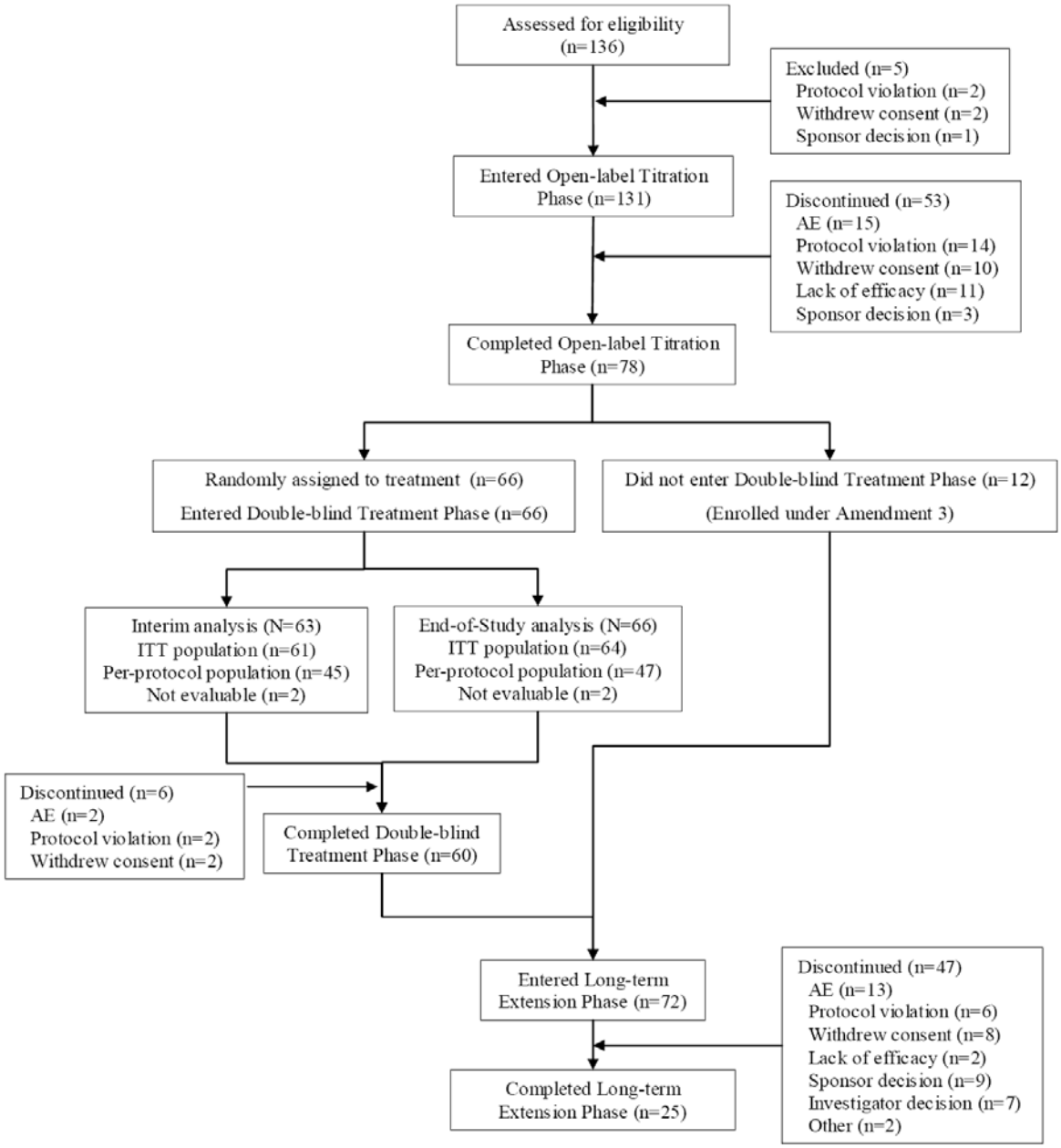
- Administrative changes
- Removal of double-blind treatment period including efficacy assessments and analysis
- Clarify patient global evaluation of medication were to be conducted at monthly study visits including the end-of-study visit

Results

Subject Disposition

Sixty-three patients entered the Double-Blind Treatment Phase prior to the interim analysis data cutoff; 2 patients were not evaluable; therefore, 61 patients were included in the interim analysis. Three additional patients entered the Double-Blind Treatment Phase after the interim analysis data cutoff. There were a substantial number of dropouts coded as “withdrew consent” that are discussed further in Appendix 9.5.

Figure 4: Flow Diagram of the Disposition of Subjects (EN3267-005)



Source: Clinical Study Report (EN3267-005), Figure 2, P. 65 of 932.

Protocol Deviations

A violation was defined as any departure to International Conference on Harmonization (ICH) or good clinical practice (GCP) guidelines or from inclusion or exclusion criteria as specified in the protocol. A deviation was defined as a departure from protocol not including GCP or inclusion or exclusion departures. Violations and deviations were to be

reported to the institutional review board (IRB) according to the IRB requirements. Protocol deviations and violations were documented by the study Investigators and reported to the IRB according to their requirements. Deviations and violations were also reported by study monitors in the monitoring visit reports and entered into a central database used by the (b) (4) clinical research department. A summary table of protocol deviations for the multiple-dose cancer BTcP studies is presented below.

Table 6: Protocol Deviations for the Multiple-dose BTcP Studies

		Dose					
	Statistic	100 mcg (N=22)	200 mcg (N=26)	300 mcg (N=58)	400 mcg (N=45)	600 mcg (N=66)	800 mcg (N=105)
At least one Protocol Deviation	N %	21 (95.5)	25 (96.2)	57 (98.3)	43 (95.6)	65 (98.5)	102 (97.1)
DIARY ERRORS - BTP EPISODES	N %	1 (4.5)	1 (3.8)	8 (13.8)	8 (17.8)	11 (16.7)	9 (8.6)
DIARY ERRORS - DOSING	N %	2 (9.1)	6 (23.1)	14 (24.1)	8 (17.8)	16 (24.2)	21 (20.0)
DIARY ERRORS - OTHER	N %	8 (36.4)	12 (46.2)	29 (50.0)	22 (48.9)	34 (51.5)	49 (46.7)
DOSING NON-COMPLIANCE	N %	7 (31.8)	10 (38.5)	27 (46.6)	22 (48.9)	34 (51.5)	53 (50.5)
DOSING NON-COMPLIANCE AND DIARY ERRORS - OTHER	N %	0	0	0	1 (2.2)	1 (1.5)	0
ECG DEVIATION	N %	1 (4.5)	4 (15.4)	11 (19.0)	5 (11.1)	13 (19.7)	15 (14.3)
ICF VIOLATION	N %	7 (31.8)	11 (42.3)	22 (37.9)	13 (28.9)	26 (39.4)	33 (31.4)
INCLUSION/EXCLUSION VIOLATION	N %	1 (4.5)	2 (7.7)	5 (8.6)	2 (4.4)	5 (7.6)	5 (4.8)
IP ISSUES	N %	3 (13.6)	3 (11.5)	10 (17.2)	5 (11.1)	9 (13.6)	10 (9.5)
LAB TEST DEVIATION	N %	7 (31.8)	8 (30.8)	18 (31.0)	11 (24.4)	24 (36.4)	30 (28.6)
LAB TEST DEVIATION AND PROCEDURE DEVIATION	N %	0	0	0	0	0	1 (1.0)
NON-COMPLIANCE WITH PROTOCOL	N %	0	0	0	1 (2.2)	0	1 (1.0)
OTHER	N %	0	2 (7.7)	2 (3.4)	2 (4.4)	2 (3.0)	0
OUT OF WINDOW DEVIATION	N %	5 (22.7)	5 (19.2)	7 (12.1)	17 (37.8)	13 (19.7)	17 (16.2)
PROCEDURE DEVIATION	N %	14 (63.6)	22 (84.6)	43 (74.1)	35 (77.8)	42 (63.6)	63 (60.0)
TOO FEW BTP EPISODES	N %	3 (13.6)	5 (19.2)	3 (5.2)	3 (6.7)	4 (6.1)	7 (6.7)
TOO MANY BTP EPISODES	N %	2 (9.1)	3 (11.5)	5 (8.6)	6 (13.3)	15 (22.7)	19 (18.1)
UNREPORTED SAE	N %	1 (4.5)	2 (7.7)	1 (1.7)	0	1 (1.5)	3 (2.9)
USE OF PROHIBITED MEDICATION OR THERAPIES	N %	1 (4.5)	1 (3.8)	5 (8.6)	2 (4.4)	6 (9.1)	4 (3.8)
VITALS DEVIATION	N %	3 (13.6)	2 (7.7)	10 (17.2)	5 (11.1)	11 (16.7)	14 (13.3)

The Applicant reported 904 deviations and 86 violations for all enrolled subjects, including patients who were screen failures. Most patients (95.5-98.5% of patients across dose groups) had at least one protocol deviation. During the double-blind treatment phase of Study EN3267-005, approximately 39 deviations/violations were recorded. The most common protocol deviations and violations were procedure

deviation (60.0%-84.6), diary errors (36.4%-51.5%), dosing noncompliance (31.8%-51.5%), and informed consent form violation (28.9%-42.3%). The procedural deviations were most often related to missing evaluations, while informed consent violations typically involved patients signing the wrong version of the informed consent form or the Health Insurance Portability and Accountability Act (HIPAA) form not being signed before study procedures were performed. Most study medication deviations related to patients' use of the diary and discrepancies in tablet count. Many deviation reports contained an additional note stating that the error resulted from subjective patient diary data and not potential study medication diversion. Protocol deviations associated with the patient diaries were followed by patient re-education on the use of the diaries and the associated assessments. Additionally, 19 patients were excluded from the per protocol (PP) population for violations, that included 15 patients who were excluded because of major violations to the titration, 4 who were excluded because of an inclusion criteria violation, and one who was excluded for taking a prohibited concomitant medication. Two patients were excluded from both the intent to treat (ITT) and PP populations: one patient for noncompliance with the diary during the Open-label Titration Phase and one patient for not using any doses during the Double-blind Treatment Phase. Patients excluded for more than one violation were listed more than once above. The Applicant considered none of these protocol deviations as serious, and stated that they did not impact upon data analysis or the conclusions.

DSI was asked to inspect two sites (Sites #539 and #530) with numerous protocol deviations and violations (72 and 163, respectively). Although the formal review of this investigation is pending at this writing, concerns were raised regarding the accuracy of electronic data capture of patient diaries due to difficulty of use by subjects. However, DSI's inspection did not reveal systematic problems or cases of drug diversion associated with medication administration discrepancy. Further, the multiple cross-over design and close supervision (daily phone calls by the investigators to each subject during the blinded study phase) minimized the influence of protocol deviations on efficacy assessments.

Demographics and Other Baseline Characteristics

The demographics of the population for this Phase 3 efficacy study (Study EN3267-005) appeared to be similar to what would be expected for the intended use of ABSTRAL. The proportions of male vs. female patients were 54.2% female and 45.8% male. Patients were predominantly Caucasian (84%), with a median age of 54 years [range 21 to 80 years]. Patient characteristics were similar for patients who completed the Open-label Titration Phase and entered the Double-blind Treatment Phase, patients who discontinued during the Open-label Titration Phase, and patients who entered the Open-Label Extension Phase.

Table 7: Demographics and Baseline Characteristics (All Treated Patients, EN3267-005)

	Completed Open-label Titration and Entered Double-blind Treatment Phase (N=66)	Discontinued During Open-label Titration Phase (N=53)	Entered Long-term Extension Phase (N=72)	Overall (N=131)
Age (years)				
n	66	53	72	131
Mean (SD)	53.3 (11.3)	56.2 (11.4)	53.6 (11.7)	55.0 (11.5)
Minimum	21	22	21	21
Median	52.0	57.0	52.5	54.0
Maximum	80	80	80	80
Age group (years), n (%)				
<18	0	0	0	0
18-64	56 (84.8)	42 (79.2)	59 (81.9)	106 (80.9)
65-74	9 (13.6)	8 (15.1)	11 (15.3)	20 (15.3)
>74	1 (1.5)	3 (5.7)	2 (2.8)	5 (3.8)
Race, n (%)				
White	56 (84.8)	43 (81.1)	61 (84.7)	110 (84.0)
Black or African American	1 (1.5)	4 (7.5)	2 (2.8)	6 (4.6)
Asian	2 (3.0)	1 (1.9)	2 (2.8)	3 (2.3)
Native Hawaiian or Other Pacific Islander	0	0	0	0
American Indian or Alaskan Native	1 (1.5)	0	1 (1.4)	1 (0.8)
Hispanic or Latino	6 (9.1)	5 (9.4)	6 (8.3)	11 (8.4)
Other	0	0	0	0
Gender, n (%)				
Female	35 (53.0)	29 (54.7)	39 (54.2)	71 (54.2)
Male	31 (47.0)	24 (45.3)	33 (45.8)	60 (45.8)

Source: Clinical Study Report (EN3267-005), Table 5, P. 71 of 932.

The demographic characteristics of the population enrolled in the open-label long-term extension study (EN3267-007) were similar to those in the Phase 3 efficacy study (Table 8).

Table 8: Demographics and Baseline Characteristics (All Treated Patients, EN3267-007)

	Completed Titration Period	Discontinued During Titration Period	Entered Maintenance Period	Overall
Age (years)				
n	96	43	96	139
Mean (SD)	56.4 (11.5)	58.3 (12.0)	56.4 (11.5)	57.0 (11.6)
Minimum	28	31	28	28
Median	57.5	60.0	57.5	58.0
Maximum	85	82	85	85
Age group (years), n (%)				
18-64	77 (80.2)	29 (67.4)	77 (80.2)	106 (76.3)
65-74	14 (14.6)	9 (20.9)	14 (14.6)	23 (16.5)
>74	5 (5.2)	5 (11.6)	5 (5.2)	10 (7.2)
Race, n (%)				
White	84 (87.5)	32 (74.4)	84 (87.5)	116 (83.5)
Black/African American	6 (6.3)	5 (11.6)	6 (6.3)	11 (7.9)
Asian	0	1 (2.3)	0	1 (0.7)
American Indian/Alaskan Native	0	1 (2.3)	0	1 (0.7)
Hispanic or Latino	6 (6.3)	4 (9.3)	6 (6.3)	10 (7.2)
Gender, n (%)				
Female	56 (58.3)	20 (46.5)	56 (58.3)	76 (54.7)
Male	40 (41.7)	23 (53.5)	40 (41.7)	63 (45.3)

Source: Clinical Study Report (EN3267-005), Table 5, P. 49 of 1166.

Treatment Compliance

The number of unevaluable BTcP episodes during the Open-label Titration Phase and Double-blind Treatment Phase in this study is summarized below (Table 9). Treatment compliance during the Open-label Titration Phase and Double-blind Treatment Phase was determined for each individual BTcP episode and was based on the dosing requirements, which specified that no more than one dose of study medication could be taken for each BTcP episode, rescue medication could be taken no sooner than 30 minutes after study medication use, there must be at least 2 hours between BTcP episodes treated with study medication, and the study medication could only be used to treat target BTcP. Treatment compliance was high during the Open-label Titration Phase; only 16 of 1001 episodes (1.6%) were considered unevaluable. During the Double-blind Treatment Phase, 14 of 393 episodes (3.6%) treated with EN3267 were unevaluable and 12 of 168 episodes (7.1%) treated with placebo were unevaluable. For both phases, the primary reason episodes were considered unevaluable was the use of rescue medication sooner than 30 minutes after treatment with study medication, followed by patients waiting less than 2 hours between episodes treated with study medication.

Table 9: Number of Unevaluable Breakthrough Episodes During the Open-label Titration Phase and Double-blind Treatment Phase (All Treated Patients)

	Open-label Titration Phase	Double-blind Treatment Phase	
	EN3267 (N=61[a])	EN3267 (N=61[b])	Placebo (N=57)
Total number of breakthrough episodes	1001	393	168
Total number of unevaluable breakthrough episodes[c], n (%)	16 (1.6)	14 (3.6)	12 (7.1)
Number of patients with at least one unevaluable breakthrough episode, n (%)	11 (18.0)	11 (18.0)	9 (15.8)
Reason for unevaluable episode[d], n (%)			
Use of rescue medication sooner than 30 minutes after study medication use	9 (14.8)	9 (14.8)	7 (12.3)
Waiting less than 2 hours between breakthrough pain episodes treated with study medication	2 (3.3)	2 (3.3)	2 (3.5)

Source: Clinical Study Protocol, Table 6, P. 73 of 932.

[a] Patients 559503 and 559502 had no diary data for the Open-label Titration Phase. These patients entered the Double-Blind Treatment Phase. Only 559502 is included in the Intent-to-Treat population.

[b] Patients 559503 and 559504 had no efficacy data from the Double-Blind Treatment Phase and were excluded from the Intent-to-Treat population.

[c] Percentages were calculated using the total number of breakthrough episodes as the denominator.

[d] A breakthrough episode might have been unevaluable for more than one reason.

Analysis of Efficacy

Primary Efficacy Endpoint: Sum of Pain Intensity Differences at 30 Minutes (SPID30). The SPID was analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment, center, sequence, and random effect for patient. Least squares means, p-values and 95% confidence intervals of the treatment difference was to be calculated.

The primary efficacy endpoint was the SPID from Baseline to 30 minutes after treating BTcP episodes with study medication during the Double-blind Treatment Phase. Results are summarized for the ITT population during the Double-blind Treatment Phase below (Table 10). For each BTcP episode, the pain score reported before taking study medication for that episode was used as baseline. Compared to placebo, the SPID was significantly improved from baseline to 30 minutes with ABSTRAL (mean difference 14.08, 95% CI, 6.515, 21.637; *P* = 0.0004). The PP analysis supported these findings.

Table 10: Mean Sum of Pain Intensity Difference at 30 Minutes After Treatment During the Double-blind Treatment Phase (ITT Population)

	EN3267 (N=61)	Placebo (N=57)
SPID at 30 minutes[a]		
n	61	57
Mean (SD)	49.5 (32.7)	36.6 (39.7)
Minimum	6.7	–17.5
Median	39.3	28.3
Maximum	138.8	150.8
Treatment comparison versus placebo[b]		
LS mean (SE)	49.30 (4.3)	35.23 (4.3)
LS mean difference	14.08	
95% CI	(6.515, 21.637)	
P value	0.0004	

Source: Clinical Study Report, Tables 7, P. 75 of 932.
Abbreviations: BTcP = breakthrough cancer pain; CI = confidence interval; ITT = intent to treat; LS = least squares; PID = pain intensity difference; SD = standard deviation; SE = standard error; SPID = sum of pain intensity difference.
[a] The SPID was calculated as the area under a patient's PID curve from each BTcP episode treated with study medication and then averaged across episodes by treatment group.
[b] The analysis used an analysis of variance model with fixed effects for treatment, pooled center, and sequence, and random effect for patient. The observed margins option in the LSMEANS statement assigned weights based on all the covariates in the model except for treatment (ie, sequence and pooled center).

Secondary Efficacy Endpoints: The secondary endpoints are presented by study in Table 11. These efficacy outcomes included: PID at 10, 15, 30, and 60 minutes; PR scores at each 10, 15, 30, and 60 minutes; TOTPAR at 30 and 60 minutes; SPID at 60 minutes; percentage of treated breakthrough pain episodes that require use of rescue medication; percentage of responders; patient global evaluation of study medication; and use of rescue medication.

Table 11: Secondary Endpoints in the ABSTRAL Clinical Program

Endpoint	Study EN3267-005 [a]		Study EN3267-007 [a]	Study SuF-002 [b]
	Double-blind period	Open-label period		
Efficacy				
PID at each time point (10, 15, 30, and 60 min) [c]	X			X
PR scores at each time point (10, 15, 30, and 60 min) [d]	X			
TOTPAR at 30 and 60 min	X			
SPID at 60 min	X			
Percent of treated BTcP episodes that require use of rescue medication	X			
Percent of responders [e]	X			
Percent of the 30% and 50% responder rates at 10 and 15 min	X			
Patient global evaluation of study medication (by visit) [f]	X	X	X	
Global pain assessment (60 min after dose)				X [g]
Rescue medication use (yes/no)	X [h]			X [h]
Quality of Life [i]				
BPI (monthly, by visit)	X	X	X	
DAPOS (monthly, by visit)	X	X	X	

Source: Clinical Overview, Table 4-2, P. 27 of 54.

[a] All efficacy assessments were collected in electronic or paper patient diaries.

[b] Paper diaries were used to collect information on efficacy assessments.

[c] Pain intensity was rated immediately prior to treating a breakthrough pain episode with study medication (ie, 0 min), and at 10, 15, 30, and 60 min (for Study EN3267-005) or 5, 10, 15, 20, and 30 min (for Study SuF-002) after treating the episode, and when rescue medication was administered (if applicable). In Study SuF-002, the PID evaluations were based on a VAS of 0 to 100 mm between the extremes of "no pain" and "worst conceivable pain." For Study EN3267-005, PID was determined by an 11-point scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine."

[d] Pain relief was rated on a 5-point scale, where 0 = no relief and 4 = complete relief. Patients were asked to indicate their answer to the following question: "How much pain relief do you have now compared to immediately prior to taking the study medication?" Pain relief was rated at 10, 15, 30, and 60 min after treating a breakthrough pain episode, and when rescue medication was administered (if applicable).

[e] Defined as patients who have at least a 30% decrease in pain intensity from Baseline to 30 min.

[f] In Study EN3267-005, patient's evaluation of current breakthrough medication was assessed at screening, 60 min after each dose during the double-blind phase or upon rescue medication use, and during the open-label, Long-term Extension Period. At the end of the double-blind phase, patients assessed satisfaction with ABSTRAL compared with

their previous breakthrough medication. In Study EN3267-007, patient's evaluation of current breakthrough medication was assessed at screening and at monthly study visits.

[g] Global pain assessment was made on a 4-point categorical scale, where the patient rated the global overall performance of the study treatment as "none," "mild," "moderate," or "excellent." The global assessment score was made 60 min after intake of study medication and was related to the entire pain episode.

[h] In case of insufficient pain relief, patients were allowed to take rescue medication 30 min after study medication intake. The patient reported the use of rescue medication by checking "yes" or "no" in the patient diary.

[i] QoL scales were administered at the screening visit, at the end of the double-blind, randomized period (Study EN3267-005 only), and at monthly visits during the open-label extension period.

Abbreviations: BPI = Brief Pain Inventory; BTcP = breakthrough cancer pain; DAPOS = Depression, Anxiety, and Positive Outlook; min = minute; PID = Pain Intensity Difference; PR = Pain Relief; QoL = Quality

The analyses of secondary endpoints were not adjusted for multiplicity and the sample sizes were relatively small, making it difficult to interpret significance levels. However, the point estimates for the secondary endpoints supported the results of the primary efficacy analysis. Compared to placebo, results favored ABSTRAL for: the SPID60; mean PID at 10, 15, 30 and 60 minutes; mean PR scores at 10, 15, 30, and 60 minutes; mean TOTPAR scores at 30 and 60 minutes; likelihood of achieving a 30% or greater reduction in pain intensity; number of episodes of BTcP requiring use of rescue medications; and the mean patient satisfaction favored ABSTRAL. Quality of life, using the BPI, and depression, anxiety and well-being, measured by the DAPOS, were also reported as improved from Screening to Visit 18.

Subpopulations: The mean SPID30 and SPID60 during the Double-blind Treatment Phase was summarized by gender, age category, type of opioid medication, and ABSTRAL dose group for the ITT and PP populations, respectively. Compared to placebo, a higher mean SPID30 and SPID60 for both genders were observed, with greater differences reported in women than men. Age was subcategorized as follows: 18 to 64 years; 65 to 74 years; and over 74 years. The majority of patients (n=52) were included in the 18 to 64 years age category, with higher mean SPIDs at both 30 (51.3 vs. 36.6) and 60 (145.7 vs. 100.6) minutes observed with ABSTRAL vs. placebo treatment groups. Although sample sizes were limited for patients in the 65 to 74 years age category (n=8), the mean SPIDs were reversed at 60 minutes after treatment. The mean SPID also was analyzed according to the type of opioid medication patients used for their background opioid analgesic (oral, transdermal, other opioid delivery systems or both oral and transdermal medication), with most patients taking an oral medication. Compared to placebo, higher mean SPIDs at both 30 minutes (48.6 vs. 35.1) and 60 minutes (140.5 vs. 99.8) were reported with ABSTRAL (35.1 and 99.8, respectively). Similar results were also observed for transdermal and other opioid delivery systems. When examined by dose categories, patients in both the 100 to 400 mcg (n=33) and 600 to 800 mcg (n=28) groups reported mean SPIDs that were greater with ABSTRAL at 30 minutes and 60 minutes. The PP subgroup analyses reported similar findings as observed in the ITT population.

On 25 September 2009 (Amendment 0005), in response to an information request by the Agency, the efficacy data for the primary endpoint and several of the secondary

endpoints were reanalyzed with the following adjustments to the previous model – inclusion of a fixed effect for episode (the period variable) and the response variable will be the SPID30 value from each episode rather than the Mean SPID. According to the Applicant, this allows up to 10 observations for each patient (1 for each episode) rather than up to 2 observations (ie, the Mean SPID30 value under treatment with ABSTRAL and the Mean SPID30 value under treatment with placebo). Additionally, the random effect is the patient nested within the sequence-by-pooled center interaction term rather than patient being the random effect. The Applicant felt that the nested random effect model is more appropriate for the trial design where each patient belongs to only one pooled center and one sequence. As in the previous analysis described above, the observed margins option in the LSMEANS statement was used to assign weights based on all the covariates in the model except for treatment (ie, episode, sequence and pooled center). Similar re-analysis were performed for SPID60, PID10, PID15, PID30, and PID60. These results are summarized in Table 12 and Table 13 below.

Table 12: Sum of Pain Intensity Difference at 30 Minutes after Treatment during the Double-blind Treatment Phase (ITT Population)

	ABSTRAL (N=61)			**Placebo (N=57)**		
SPID at 30 minutes[A]	N	Mean	SD	N	Mean	SD
Descriptive Statistics						
BTcP Episode 1	43	48.7	38.9	18	33.1	46.9
BTcP Episode 2	36	45.5	38.8	19	22.2	41.6
BTcP Episode 3	38	48.8	44.1	18	34.3	46.2
BTcP Episode 4	35	50.0	46.9	22	62.3	54.8
BTcP Episode 5	38	49.1	43.7	18	54.4	53.9
BTcP Episode 6	40	58.8	49.2	16	21.3	26.3
BTcP Episode 7	40	52.2	39.7	16	35.2	41.1
BTcP Episode 8	39	54.1	47.0	16	17.6	34.3
BTcP Episode 9	40	57.9	43.5	14	29.4	57.0
BTcP Episode 10	41	43.2	42.5	9	62.1	61.8
Treatment comparison vs placebo[B]						
LS Mean (SE)	50.43 (3.64)			35.84 (4.16)		
ABSTRAL – Placebo (95% CI)	14.58 (8.45- 20.72)					
p-value	<0.0001					
Estimated exact p-value[C]	<0.0001					

Source: Amendment 0005, Table 2, P. 7 of 10.
[A] The SPID was calculated as the area under a patient's PID curve for each BTcP episode treated with ABSTRAL.
[B] The analysis used an analysis of variance model with fixed effects for treatment, sequence, episode, pooled center, and a random effect for patient. The observed margins option in the LSMEANS statement assigned weights based on all the covariates in the model except for treatment (ie, episode, sequence and pooled center).
[C] The exact p-value was estimated using 50 000 simulations of the randomization.
Abbreviations: BTcP = breakthrough cancer pain; CI = confidence interval; ITT = intent to treat; LS = least squares; PID = pain intensity difference; SD = standard deviation; SE = standard error; SPID = sum of pain intensity difference.

Table 13: Comparison of the Analysis Results (ITT Population)

Variable	Previous Analysis		Current Reanalysis		
	ABSTRAL – Placebo	P-value[B]	ABSTRAL – Placebo	P-value[C]	Exact P-value[D]
SPID30[A]	14.08	0.0004	14.58	<0.0001	<0.0001
SPID60[A]	41.61	0.0002	42.98	<0.0001	<0.0001
PID10	0.28	0.0055	0.27	0.0062	0.0144
PID15	0.55	0.0011	0.58	<0.0001	<0.0001
PID30	0.87	0.0002	0.93	<0.0001	<0.0001
PID60	0.98	0.0004	0.53	0.0026	0.0019

Source: Amendment 0005, Table 2, P. 6 of 10. Movement

[A] The SPID was calculated as the area under a patient's PID curve for each BTcP episode treated with study medication.

[B] The previous analysis used an analysis of variance model with fixed effects for treatment, sequence, pooled center, and a random effect for patient, and the mean of all episodes per treatment within a patient as the response variable.

[C] The current reanalysis used an analysis of variance model with fixed effects for treatment, sequence, episode, pooled center, and a random effect for patient, and the endpoint value at each episode as the response variable.

[D] The exact p-value was estimated using 50 000 simulations of the randomization

Abbreviations: ITT = intent to treat; PID = pain intensity difference; SPID = sum of pain intensity difference; BTcP = breakthrough cancer pain.

Supporting Studies

Study SuF-002. The pharmacodynamics of ABSTRAL with regard to PID was evaluated in this Phase 2, randomized, multicenter, double-blind, four-period crossover study (placebo, 100, 200, and 400 ug ABSTRAL), with primary comparison of ABSTRAL 400 mcg versus placebo in opioid tolerant patients with locally advanced or generalized cancer. The Applicant reported overall improvement in PID, the primary efficacy endpoint, for ABSTRAL 400 mcg as compared with placebo (8.57 mm, p = 0.0001), with differences observed at 15 and 20 minutes after treatment. The number of patients using additional rescue medication was lower and overall global performance favored ABSTRAL 400 mcg over placebo. A post-hoc analysis was performed to provide descriptive statistics for the SPID30 for each of the doses of ABSTRAL (100, 200 and 400 mcg) tested in that trial. At 30 minutes after treatment, BTcP episodes treated with ABSTRAL 400 mcg (LS mean 62.10) was reported as significantly different (p = 0.0102; 95% CI for difference in means, 5.16 - 36.94) than placebo (LS mean 41.05). The SPID30 for the 100 and 200 mcg doses were not statistically different from placebo.

Study EN3267-007. The efficacy of ABSTRAL was not formally assessed in Study EN3267-007, which evaluated the long-term safety and effectiveness of ABSTRAL in treating BTcP episodes in opioid tolerant cancer patients who were using stable doses of opioid medication. However, the Applicant reported the results from the patient's global evaluation of ABSTRAL and quality of life (QoL) instruments. At screening, prior to ABSTRAL administration, 12.3% (16/139 patients) and 41.5% (54/139 patients) who completed the evaluation were very satisfied or satisfied, respectively, with their current (non-ABSTRAL) medication. Of the 92 patients who attended the final visit (Visit 14/End-of-Study), 34.8% (32 patients) were very satisfied and 42.4% (39 patients) were satisfied with ABSTRAL for the treatment of BTcP. The BPI and DAPOS QoL measures were also assessed in 85 patients during this study. When asked if any pain (other than minor pain) was experienced that day (BPI Item 1), 82 (96.5%) patients responded "yes" at Screening compared with 57.6% at the final visit. Patients also reported some reduction in the interference of pain on general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life (BPI Item 9). A reduction (i.e., improvement) in depression and anxiety scores compared with Screening at each monthly visit also was observed using the DAPOS questionnaire.

Discussion of Efficacy Findings

The Applicant's analysis of the primary endpoint (SPID30) for Study EN3267-005 supports the finding of efficacy for ABSTRAL compared to placebo for the treatment of BTP in patients with malignancies receiving around-the-clock opioid therapy for cancer pain. The data appears to be rugged, with similar results reported ($p<0.0001$) using the analytical model recommended by the Agency and confirmed by Dr. Yan Zhou. The Division of Biometrics II concluded that the study successfully demonstrated the superiority of ABSTRAL over placebo as measured by the SPID30.

Analysis of Safety

There were 29 deaths, 73 SAES, and 67 adverse events that led to discontinuation in the Applicant's clinical development program (Studies: EN3267-001; EN3267-003; EN3267-005; EN3267-007; EN3267-013; 2246-EU-004; 2246-EU-005; SUF-001; SUF-002). A complete discussion of the safety of this product is presented in Section 7.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is the management of breakthrough pain (BTP) in patients with cancer who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their persistent cancer pain.

6.1.1 Methods

Evidence for the efficacy of ABSTRAL comes from a single study, EN3267-005; a double-blind, placebo-controlled evaluation of the efficacy, safety, and tolerability of ABSTRAL in the treatment of BTP in cancer subjects. The Division considered submission of a single adequate and well-controlled efficacy study in the context of previous Agency findings for fentanyl acceptable for this NDA submission.

Study SuF-002 (Phase 2) and EN3267-007 (open-label safety study) provide support for the efficacy findings demonstrated in EN3267-005.

6.1.2 Demographics

The population for the Phase 3 efficacy study (Study EN3267-005) included 54.2% females, and was predominantly Caucasian (84%) with a median age of 54 years. Patient characteristics were similar across study phases. Since there are no known race-based differences in safety or efficacy for fentanyl, the Caucasian predominance is acceptable.

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint: Sum of Pain Intensity Differences at 30 Minutes (SPID30). The SPID30 was analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment, center, sequence, and random effect for patient. Least squares means, p-values and 95% confidence intervals of the treatment difference was to be calculated.

The primary efficacy endpoint was the SPID from Baseline to 30 minutes after treating BTcP episodes with study medication during the Double-blind Treatment Phase. Results from the reanalysis of the primary outcome are summarized for the ITT population during the Double-blind Treatment Phase in Table 12. For each BTcP episode, the pain score reported before taking study medication for that episode was used as baseline. Compared to placebo, the SPID was significantly improved from

baseline to 30 minutes with ABSTRAL (mean difference 14.58, 95% CI, 8.45, 20.72; *P* < 0.0001).

6.1.5 Analysis of Secondary Endpoints(s)

Results from analyses of secondary endpoints favor ABSTRAL over placebo and support the primary efficacy analysis. However, small sample sizes and failure to adjust for multiplicity limit the interpretability of these results.

End-of-Study Analyses

End-of-Study efficacy analyses included 3 additional patients who were included in the ITT population who participated in the Double-blind Treatment Phase of the study at the time the interim analysis, but had not yet completed the blinded phase of the study. This efficacy analyses included data from all 64 patients included in the ITT population for this study. As with the interim analysis, the SPID30 was significantly higher with ABSTRAL compared to placebo (*P* = 0.0004; 95% CI for difference in means, 7.003-22.964). As anticipated, results from inclusion of the 3 remaining patients were similar to those from the interim analyses. These analyses were performed prior to the reanalysis of the SPID30 submitted with Amendment 0005 on 25 September 2009. Reanalysis of these data by Dr. Yan Zhou resulted in similar findings with a difference from placebo in LS Means of 16 (95% CI 10, 22; *P* < 0.0001).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No specific exposure-response assessments were performed. The multiple-dose studies in cancer patients (Studies EN3267-005 and EN3267-007) are the most relevant to the proposed indication for treatment of BTcP and proposed dosing recommendations to titrate patients to a safe and effective dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term assessment of efficacy was a secondary outcome for both Phase 3 studies (Studies EN3267-005 and EN3267-007). Approximately 90% of the 92,986 episodes of BTcP reported were treated with ABSTRAL. Of the 156 patients who attended the End-of-Study visit, 64.7% reported some satisfaction with their pain relief compared to baseline evaluation in which 54% reported satisfaction with their current medication.

6.1.10 Additional Efficacy Issues/Analyses

Re-analysis of the primary and secondary efficacy endpoints was submitted by the Applicant (25 September 2009) in response to the information request by the statistical reviewer, and resulted in similar findings for the primary and secondary outcomes. Refer

to Amendment #5 and the Statistical review performed by Dr. Yan Zhou of the Division of Biometrics II for detailed description of these analyses and findings.

7 Review of Safety

Safety Summary

7.1 Methods

Sixteen clinical studies have been conducted with ABSTRAL, and included: one adequate, well-conducted efficacy and safety study in opioid-tolerant cancer patients, one Phase 3 long-term safety and effectiveness study in cancer patients, one Phase 2 pharmacodynamic study in cancer patients, five Phase 1 pharmacokinetic studies, five Phase 1 bioavailability studies, and three Phase 1 bioequivalence studies. The two Phase 3 studies (EN3267-005 and EN3267-007) form the basis for the safety assessment of ABSTRAL.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

EN3267-005 was a randomized, double-blind, placebo-controlled, multiple cross-over study comparing ABSTRAL with placebo for the treatment of breakthrough pain in subjects with cancer receiving a stable opioid regimen for persistent pain. Eligible subjects were titrated to an effective dose (100 µg to 800 µg) of ABSTRAL in an open-label period (up to two weeks in duration). Subjects who identified an effective dose of ABSTRAL entered the double-blind placebo controlled treatment period of the study. During this period (up to two weeks in duration), subjects randomly received ten study drug doses (7 as ABSTRAL, and 3 as placebo) to treat breakthrough pain episodes at the dose found effective for that subject during the titration period. Subjects had three to four clinic visits over an approximate four-week span.

EN3267-007 is an ongoing, open-label, multi-center study evaluating the safety of ABSTRAL in adult subjects with cancer pain using a stable scheduled oral opioid regimen. Subjects are eligible to enter following successful completion of EN3267-005, or directly if they met the same entry criteria as EN3267-005. Subjects entering directly are titrated to an effective dose (100 µg to 800 µg) in a similar manner to the one used in EN3267-005. Once a dose has been identified, subjects will continue at that dose for an unlimited period, with dosage adjustments allowed as required to control breakthrough pain. Throughout the study, all subjects return to the clinic monthly for safety assessments, dosage adjustment, and dispensing of additional study medication.

120 DAY SAFETY UPDATE

On 3 December 2009, the Applicant submitted the Day 120 safety update (Amendment 0009), acknowledging that no new interventional clinical studies have been initiated by ProStrakan since submission of the NDA in August 2009, and no such studies are currently ongoing. One unexpected SAE was reported on 4 November 2009 from the United Kingdom (IND 69,190) related to the occurrence of glossitis, stomatitis, oral pain, and edema of the mouth in a 63 year-old female. Although causality was not assessed, spontaneous reports to the Applicant are classified as possibly related. The SAE was initially treated with antihistamines, but additional follow-up information was not provided.

The 120 safety update also included a summary of the updated postmarketing safety data. Details regarding post-marketing surveillance and attainment of safety data via Periodic Safety Update Reports (PSURs) are provided in Section 8 Postmarket Experience.

The Safety Update does not change my overall impression of the adverse event profile of ABSTRAL.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 8.0. The appropriateness of the Applicant's coding was evaluated by comparing the preferred terms to the verbatim terms recorded by investigators. Coding was reasonably accurate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Studies were pooled and analyzed based on whether they enrolled cancer patients or healthy subjects, and then further subcategorized according to single dose and multiple-dose studies. Healthy volunteers who were pre-treated with naltrexone to minimize opioid-related AEs were analyzed separately from studies in which healthy subjects did not receive naltrexone. Safety conclusions by the Applicant were drawn primarily from the most relevant patient population (multiple-dose studies in cancer patients).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to ABSTRAL included 694 subjects that received at least a single dose, of which 383 were healthy volunteers and 311 were cancer patients. Table 14

summarizes the number of subjects exposed to single and multiple doses in the Applicant's clinical development program.

Table 14: Summary of Subjects Exposed to at Least a Single Dose of ABSTRAL

Number of Subjects					
Multiple-dose Studies in Cancer Patients	**Single-dose Studies in Cancer Patients**	**All Studies in Cancer Patients**	**Single-dose Healthy Subject Studies with Naltrexone**	**Single-dose Healthy Subject Studies without Naltrexone**	**Multiple-dose Healthy Subject Studies**
270	41	311	226	147	82

Source: Integrated Summary of Safety, Table 1-4, P. 40 of 156.

In the entire population, 342 subjects (41 with cancer and 301 healthy volunteers) received only a single dose of ABSTRAL, while 352 subjects (270 with cancer and 82 healthy volunteers) received multiple doses. Cancer patients in the multiple-dose BTcP studies were exposed from 1 to 405 days (mean 40.2-124.2 days; median 6.5-55 days) to doses of 100 to 800 mcg of ABSTRAL. In this population, prior and concomitant medication use and baseline demographics across individual dose groups were similar, of which the mean age ranged from 53.5 to 59.4 years, females represented 46.7%-59.1% of patients, 72.7%-90.5% were classified as Caucasian, and the mean body mass index (BMI) ranged from 26.03 to 29.22 kg/m^2. Prior and concomitant medication use in the multiple-dose cancer studies was also similar across individual dose groups and study phases. Demographics of the multiple-dose cancer patient population are presented below (

Table 15).

Table 15: Demographic and Baseline Characteristics by Dose – Multiple-dose Studies in Cancer Patients

	Dose					
	100 µg (N=22)	**200 µg (N=26)**	**300 µg (N=58)**	**400 µg (N=45)**	**600 µg (N=66)**	**800 µg (N=105)**
Age (years)						
Mean (SD)	59.4 (7.85)	57.9 (10.50)	53.5 (12.34)	56.7 (9.67)	55.8 (11.40)	54.4 (11.67)
Range	40 – 74	44 – 85	21 – 79	39 – 78	21 – 78	25 – 81
Age group (years), n (%)						
17-64	17 (77.3)	20 (76.9)	45 (77.6)	37 (82.2)	51 (77.3)	86 (81.9)
≥ 65	5 (22.7)	6 (23.1)	13 (22.4)	8 (17.8)	15 (22.7)	19 (18.1)
≥ 75	0	3 (11.5)	1 (1.7)	2 (4.4)	4 (6.1)	5 (4.8)
Gender, n (%)						
Male	9 (40.9)	12 (46.2)	25 (43.1)	24 (53.3)	27 (40.9)	46 (43.8)
Female	13 (59.1)	14 (53.8)	33 (56.9)	21 (46.7)	39 (59.1)	59 (56.2)
Race, n (%)						
White/Caucasian	16 (72.7)	22 (84.6)	46 (79.3)	35 (77.8)	55 (83.3)	95 (90.5)
Japanese	0	0	0	0	0	0
Black	2 (9.1)	1 (3.8)	4 (6.9)	4 (8.9)	5 (7.6)	4 (3.8)
Asian	0	0	2 (3.4)	2 (4.4)	1 (1.5)	0
Other	4 (18.2)	3 (11.5)	6 (10.3)	4 (8.9)	5 (7.6)	6 (5.7)
Height (cm)						
Mean (SD)	164.74 (9.582)	169.91 (11.447)	167.08 (11.373)	168.75 (11.132)	167.59 (11.011)	169.42 (10.797)
Range	147.3 – 183.0	150.5 – 188.0	146.0 – 193.0	150.0 – 188.0	146.0 – 193.0	147.0 – 193.0
Weight (kg)						
Mean (SD)	79.65 (19.126)	75.01 (15.005)	76.37 (23.271)	81.49 (19.387)	77.51 (18.978)	78.35 (20.164)
Range	45.0 – 118.2	55.3 – 113.9	42.4 – 137.0	43.7 – 131.9	37.5 – 126.8	44.9 – 129.0
BMI (kg/m^2)						
Mean (SD)	29.22 (6.508)	26.03 (5.617)	27.10 (7.276)	28.60 (7.474)	27.52 (6.736)	27.43 (6.358)
Range	18.0 – 44.6	17.9 – 36.2	16.8 – 45.5	16.5 – 49.7	17.6 – 52.8	18.8 – 49.7

Source: Integrated Summary of Safety, Table 1-8, P. 40 of 156.
Abbreviations: SD, standard deviation.
Note: The sample sizes in each individual dose group sum to more than the 270 enrolled patients because patients may have been assigned to different individual dose groups
during different phases of the studies.

7.2.2 Explorations for Dose Response

Because patients were individually titrated to an optimal balance between efficacy and adverse events, this is not applicable to this application.

7.2.3 Special Animal and/or In Vitro Testing

During the review process, as requested by the Agency, the Applicant submitted a final report (7 October 2009) examining the clastogenic potential of the fentanyl analog (b) (4). By evaluating the effects (b) (4) on the chromosomes of cultured human peripheral blood lymphocytes in two independent experiments, the Applicant concluded that this impurity did not induce structural chromosome aberrations when tested to the limit of cytotoxicity.

There was no other special animal or *in vitro* testing carried out in this development program.

7.2.4 Routine Clinical Testing

The routine clinical testing performed in the ABSTRAL development program appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is not applicable since this is a 505(b)(2) application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Since ABSTRAL was being dosed against a background of around-the-clock opioids (with similar adverse event profiles to the study drug), explorations for potential adverse events for similar drugs in this drug class were not conducted.

7.3 Major Safety Results

I reviewed the major safety results. Recognizing the confounding and limitations in evaluating this kind of product, I found no major safety findings that appeared attributable to the drug product. Rather, the major safety findings were consistent with opioids, the concomitant medications, and the general debilitated condition of the patients enrolled in the trials.

7.3.1 Deaths

Deaths during the clinical trials of ABSTRAL were expected due to the nature of the patient population (cancer patients, often terminal). A total of 29 deaths occurred during

the development program, all during the multiple dose studies in cancer patients (10 during EN3267-005). Most of the deaths (21 patients) were attributed cancer progression, and none were reported as treatment-related. Other causes of death included infections (2 patients), suicide (1 patient), cardiac arrest (1 patient), renal failure (2 patients), intestinal obstruction (2 patients). The suicide was considered not related to the study medication. Information provided by the Applicant, which included CRFs, narratives, and data listings, were reviewed for each death. A comparison of death rates between treatment and placebo was not possible due to the repeat dose, multiple cross-over design of EN3267-005 and open-label design of EN3267-007.

Deaths on the Day of Study Drug Administration

Four of the 29 patients who died received study drug on the day of their deaths, and the date of the last study dose of an additional patient was not specified. The relationship of the time of last dose to the time of death was not generally available for these patients. Six deaths were reported during the open-label titration phases (EN3267-005 and EN3267-007), of which one death occurred on the same day as ABSTRAL administration. The case narrative for this patient is as follows:

Patient No.: 723701
Case No(s).: 2007EO000019
Event(s): Prostate cancer metastatic; azotemia; renal failure acute
Event Category(ies): Death; SAE; discontinuation due to an AE
Relationship(s) to Study Drug: Not related
This 68-year-old male took EN3267 as needed starting on 16 Apr 2007 for episodes of breakthrough cancer pain and was taking 600 mcg sublingual tablets during the open-label titration phase of the study. The patient's medical history included actinic keratosis, seborrheic dermatitis, multiple filled cavities, pulmonary nodule, tobacco abuse, deep vein thrombosis, hypertension, increased cholesterol, soft right carotid bruit, venous insufficiency, constipation, diarrhea, diverticulosis, gastroesophageal reflux disease, laryngeal reflux, nausea, rectal pain, cachexia, decreased appetite, decreased calcium, dehydration, hyperkalemia, hypokalemia, metastatic small cell carcinoma of the prostate, weight loss, acute renal failure, benign prostatic hypertrophy, bilateral hydronephrosis, bilateral nephrostomy stents, neurogenic bladder, pyelonephritis, recurrent urinary tract infections, ureteral obstruction, numbness of left hand fourth and fifth digits, radiation therapy, anemia, blood transfusion, leukocytosis, neutropenia, chronic back pain, degenerative joint disease, lumbago, hepatic mass, depression, cancer pain secondary to metastatic prostate cancer, pelvic lymph node dissection and septal repair. The patient's concomitant medications included acetaminophen, calcium and vitamin D, docusate, epoetin not otherwise specified, ferrous sulfate, furosemide, hydrocodone and acetaminophen, magnesium hydroxide, megestrol, metoclopramide, metoprolol, morphine, omeprazole, ondansetron, piperacillin and tazobactam, *Plantago afra*, potassium chloride, prochlorperazine, *Senna alexandrina*, sodium bicarbonate, sulfamethoxazole/trimethoprim, terazosin and

warfarin. On (b) (6) the subject presented to the emergency room because he had been experiencing a lack of energy, poor oral intake and decreased dark urine output for 4 days. Subsequently, the patient was hospitalized for severe renal failure acute, severe azotemia and severe metastatic prostate cancer. The acute renal failure was treated with sodium bicarbonate. The patient and his family decided to proceed with comfort measures only, and study drug was discontinued. The renal failure acute was ongoing at the time of the patient's death. This patient took his last study drug dose on 07 May 2007 and discontinued from the study the same day. He discontinued from the study because metastatic prostate cancer and the azotemia. On (b) (6) the patient died because of the metastatic prostate cancer and the azotemia. An autopsy was not performed; the death certificate listed the final cause of death as metastatic prostate cancer, uremia and cardiopulmonary arrest. The investigator considered the renal failure acute, azotemia and the metastatic prostate cancer related to the patient's concurrent illness. The medical monitor considered the renal failure acute and azotemia related to the patient's genitourinary obstructive disease and the metastatic prostate cancer related to the natural course of the disease. None of the SAEs were considered related to study drug.

Although there is inadequate information to determine the cause of death in this patient, progression of his underlying illness is a likely etiology, and the events of metastatic prostate cancer, uremia and cardiopulmonary arrest were probably related to the patient's concurrent illness.

Two additional deaths occurred on the same day of ABSTRAL administration during the open-label maintenance phase of the study. The narratives for these patients were as follows:

Patient No.: 732701
Case No(s).: 2006EO000010; 2006EO000015; 2006EO000021
Event(s) Prostate cancer metastatic; anemia; dehydration; anemia (Received as 3 separate reports)
Event Category(ies) Death; SAE; discontinuation due to an AE
Relationship(s) to Study Drug Not related; unlikely related
This 68-year-old male took EN3267 as needed starting on 28 Jun 2006 for episodes of breakthrough cancer pain and was taking 100 mcg sublingual tablets during the maintenance phase of the study. The patient's medical history included scattered ecchymoses, scattered senile purpura, allergic rhinitis, glaucoma, headaches, sinus congestion, dyspnea on exertion, grade 2/6 systolic murmur, hypercholesterolemia, hypertension, ischemic heart disease, tachycardia, colonoscopy, constipation, diverticular disease, hemorrhoids, nausea, obese abdomen, occult-positive stools, elevated glucose, prostate cancer, Guillain-Barré syndrome, anemia arthroscopic surgery right knee, barrel chest, bone metastasis, generalized pain, kyphosis, leg cramps, mild carpal tunnel syndrome, osteoarthritis, osteopenia, plantar fascitis, probable tendinitis right elbow, fatty liver, positive hepatitis B antigen/antibody tests, and

lower back pain secondary to prostate cancer. The patient's concomitant medications included acetaminophen, amlodipine, atenolol, cetirizine, darbepoetin alfa, enalapril, estradiol, fenofibrate, fentanyl, finasteride, goserelin, hydrochlorothiazide, ketoconazole, lorazepam, morphine, rabeprazole, timolol and zoledronic acid. On (b) (6) the patient was hospitalized for severe anemia and dehydration, presenting with profound generalized weakness. He reported protracted vomiting and that he was unable to keep even water down over the past week. It was noted that he received a blood transfusion approximately 2 weeks before and was to be seen by a gastroenterologist for evaluation of several recent heme-positive stools. Results of laboratory tests collected upon admission were significant for white blood cell count (WBC) 3.3 × 109/L (reference range: 4.1-10.9 × 109/L), absolute neutrophil count 1.9 × 109/L (reference range: 1.4-9.5 × 109/L), hemoglobin 7.4 g/dL (reference range: 13.0-17.0 g/dL), hematocrit 22.6% (reference range: 39.0%-51.0%) and platelet count 51 × 109/L (reference range: 150-400 × 109/L). Chest x-ray revealed nodular densities suspicious for metastatic lesions, and post-surgical changes within the pelvis and heterogeneity of the bony density, which raised the suspicion of bone metastasis. On (b) (6) the patient underwent an upper gastrointestinal endoscopy, which revealed a hiatal hernia and small petechiae in the esophagus but no active inflammatory changes or bleeding. Computed tomography (CT) scan of the abdomen and pelvis on that same day showed extensive osseous metastases involving the ribs, spine, bones of the pelvis and proximal femurs, a nodal mass in the retroperitoneum, post-radiation changes in the pelvis and multiple renal cysts. Treatment included intravenous fluids, packed red blood cells, corticosteroids, oprelvekin, platelet transfusion and filgrastim. On (b) (6) the patient's laboratory results included WBC 6.1 × 109/L, absolute neutrophil count 4.8 × 109/L, hemoglobin 10.5 g/dL , hematocrit 30.2% and platelet count 50 × 109/L. On (b) (6) the anemia and dehydration were resolved, and the patient was discharged from hospital. On (b) (6) the patient was hospitalized again for severe anemia. Results of laboratory tests collected upon admission were significant for WBC 2.8 × 109/L, absolute neutrophil count 1.7 × 109/L, hemoglobin 6.6 g/dL, hematocrit 20.5% and platelet count 23 × 109/L. After the patient experienced a syncopal episode while hospitalized, a CT scan and magnetic resonance imaging were done with results suggestive of metastatic disease with associated hemorrhage. Treatment during hospitalization included intravenous fluids, dexamethasone, packed red blood cells and platelets. On (b) (6) the anemia was resolved, and the patient was discharged from hospital. The patient began to receive home hospice services on (b) (6), and on (b) (6) the patient suffered metastatic prostate cancer (progression of prostate cancer) of severe intensity and died at home. This patient took his last study drug dose on 14 Sep 2006 and discontinued from the study the same day. He discontinued from the study because of the metastatic prostate cancer. On (b) (6) the patient died because of the metastatic prostate cancer. The death certificate listed the cause of death as cardiopulmonary arrest due to metastatic prostate cancer. An autopsy was not performed. The investigator considered the first event of anemia and the dehydration unlikely to be related to study drug and the second event of anemia and the metastatic prostate cancer related to concurrent illness and not related to study drug. The medical

monitor considered the first event of anemia most likely related to the patient's underlying cancer and possible occult gastrointestinal blood loss and poor marrow production capacity resulting from previous multiple radiation and chemotherapy treatment, the dehydration related to the pre-existing "protracted vomiting" and the patient's inability to tolerate much oral intake, the second event of anemia related to underlying metastatic prostate cancer with probable existing depressed bone marrow production and exacerbation of pre-existing anemia and the metastatic prostate cancer related to the natural course of the cancer and all of the SAEs not related to study drug.

There is inadequate data available to determine the cause of this subject's cardiopulmonary arrest and death. Although study medication could have been associated with vomiting and resultant dehydration, pre-existing protracted vomiting is a possible etiology. In concurrence with the medial monitor, the anemia, metastatic prostate cancer, and occult gastrointestinal blood loss and poor marrow production capacity were probably unrelated to study medication.

Patient No.: 809701
Case No(s).: 2008EO000031
Event(s) Intestinal obstruction
Event Category(ies) Death; SAE; discontinuation due to an AE
Relationship(s) to Study Drug Not related

This 54-year-old male took EN3267 as needed starting on 29 May 2008 for episodes of breakthrough cancer pain and was taking 800 mcg sublingual tablets during the maintenance phase of the study. The patient's medical history included hypertension, constipation, dysphagia, gastroesophageal reflux disease, metastatic esophageal cancer, nausea, vomiting, loss of appetite, weight loss, erectile dysfunction, urinary frequency, intravenous substance abuse, alcohol abuse, tobacco use, abdominal lymphadenopathy, hepatitis B, hepatitis C, hepatomegaly, portal vein thrombosis, allergy to iodine, anxiety and epigastric and upper abdominal pain related to cancer. The patient's concomitant medications included azithromycin, bisacodyl, chlorpromazine, dexamethasone, doxazosin, famotidine, fentanyl, furosemide, glycopyrronium, haloperidol, hydromorphone, hyoscine, lactulose, lorazepam, macrogol, metoclopramide, midazolam, normal saline and potassium chloride, ondansetron, prochlorperazine, rabeprazole, ranitidine, sennosides and docusate, sodium chloride, tamsulosin, trazodone, vitamin K and zolpidem. On (b) (6) the patient enrolled into hospice care because of his diagnosis of metastatic esophageal cancer. The patient received treatment at an inpatient hospice facility for nausea and vomiting from (b) (6) at which time he was diagnosed with a partial bowel obstruction secondary to his metastatic disease. On (b) (6) the patient again presented to the inpatient hospice facility with acute onset of severe abdominal pain, nausea, vomiting and hematemesis. Subsequently, the patient was diagnosed with a complete intestinal obstruction secondary to metastatic esophageal cancer. Treatment included hydromorphone, ondansetron, lorazepam, midazolam and intravenous glycopyrrolate. The study drug was permanently discontinued. Despite treatment, the patient's condition declined rapidly. On (b) (6) the patient expired. The site

reported that an autopsy was not performed, and a death certificate was not obtained. This patient took his last study drug dose on 12 Jul 2008 and discontinued from the study on the same day. He discontinued from the study because of the intestinal obstruction and death. The investigator considered the intestinal obstruction secondary to metastatic esophageal cancer related to concurrent illness and not related to study drug. The medical monitor considered related to metastatic esophageal cancer and not related to study drug.

Although study medication could have been associated with severe nausea and vomiting, and there is inadequate information to determine the cause of death, these events and death were probably related to the patient's underlying disease.

Deaths Occurring During the Open-Label Titration Phase

The open-label titration phase, prior to dose stabilization, is the study phase where subjects could be more vulnerable to SAEs related to excessive doses of study medication. Five deaths occurred during this study phase between 8 and 59 days after the last ABSTRAL dose. The narratives are as follows:

Patient No.: 548505
Case No(s).: 2006EO000030
Event(s): Non-small cell lung cancer metastatic
Event Category(ies): Death, SAE, discontinuation due to an AE
Relationship(s) to Study Drug: Not related
This 63-year-old male took EN3267 as needed starting on 24 Oct 2006 for episodes of breakthrough cancer pain and was taking 600 mcg sublingual tablets during the open-label titration phase of the study. The patient's medical history included difficulty with vision, metastatic lung cancer, nausea, neuropathy, anemia, spleen metastasis, cancer related right flank pain, degenerative disc disease, osteoarthritis, allergies to codeine and morphine, extreme fatigue and insomnia. The patient's concomitant medications included bevacizumab, cyanocobalamin, dexamethasone, fentanyl, folic acid, gemcitabine, hydromorphone, ketorolac tromethamine, lorazepam, metoclopramide, ondansetron, oxycodone, palonosetron and pemetrexed. On 01 Nov 2006 the investigator reported that the patient had been suffering from anorexia for (b) (6) and he was hospitalized for the event of severe non-small cell metastatic lung cancer. The patient was discontinued from the study because of the SAE. During the patient's hospitalization, he suffered from worsening jaundice, failure to thrive, malnutrition and inadequate pain control. The patient took his last study drug dose on 28 Oct 2006. The patient was advised of his grave prognosis, and he opted for no further aggressive management. On (b) (6) the patient was transferred to hospice for terminal care. On (b) (6) the patient died due to the metastatic non-small cell lung cancer. An

autopsy was not performed, and the cause death was listed on the death certificate as metastatic lung cancer. The investigator considered the non-small cell cancer metastatic related to the patient's concurrent illness and not related to study drug. The medical monitor considered the non-small cell cancer metastatic related to the patient's underlying metastatic cancer.

Since death in this patient occurred 14 days after the last dose of study medication, death and the SAE appear to be unrelated to study drug. It also is likely that worsening jaundice, failure to thrive, and malnutrition were due to his concurrent illness. Although the patient received hydromorphone with a known history of allergy to codeine and morphine, death was likely related to the underlying disease.

Patient No.: 569501
Case No(s).: 2007EO000041
Event(s): Esophageal cancer metastatic; vomiting
Event Category(ies): Death, SAE; discontinuation due to an AE
Relationship(s) to Study Drug: Not related; possibly related
This 58-year-old male took EN3267 as needed starting on 18 Jul 2007 for episodes of breakthrough cancer pain and was taking 100 mcg to 300 mcg sublingual tablets during the open-label titration phase of the study. The patient's medical history included alopecia/hair loss, moles, decreased hearing left ear, intermittent aspiration, intermittent hoarseness, chronic obstructive pulmonary disease, metastatic carcinoma lungs, left sided superior vena cava, tachycardia, bad breath, Barretts esophagus, belching, carcinoma esophagus, duodenal ulcers, duodenitis, esophagogastroduodenoscopy for recurrent vomiting after surgery, esophageal discomfort, esophageal mass, esophageal ulcers, esophagitis, gastric bezoar, gastric paresis, gastritis, gastroesophageal reflux disease, hiatal hernia, partial esophagectomy and gastric pull through and anastomosis, Schatzki ring, hypoalbuminemia, weight loss, urination at night, anemia, leukopenia, chest wall pain, degenerative joint disease in spine, joint pains, right upper back pain, high alkaline phosphatase, metastatic carcinoma of the liver and itching/allergies in eyes. The patient's concomitant medications included cisplatin, dexamethasone, dolasetron, doxorubicin, etoposide, hydrocodone and acetaminophen, lansoprazole, mannitol, metoclopramide, morphine, ondansetron, palonosetron and potassium chloride. On 19 Jul 2007 the patient experienced an episode of vomiting, dizziness and tachycardia of moderate intensity and nausea of severe intensity, all of which resolved 1 to 3 hours later. Study drug was discontinued because of the vomiting. On (b) (6) the patient was hospitalized after complaining of excruciating pain in his back and spine. He presented with complaints of intermittent hoarseness accompanied by aspiration of fluid, significant weight loss, appetite loss, constipation, occasional nausea and vomiting with an episode of coffee ground emesis thought to be related to gastrointestinal bleed and tenderness at the spinal level of T4 through T10. Diagnoses included a new

paravertebral metastasis at T3 with associated cord compression and fracture. Treatment recommendations included palliative radiation at the level of T3 and endoscopy for an upper gastrointestinal bleed. During hospitalization, he also experienced septicemia. Treatment included total parenteral nutrition, antibiotic therapy including metronidazole and vancomycin for sepsis, intravenous cefepime for positive blood cultures and increased dosing of intravenous hydromorphone and morphine for pain control. On (b) (6) the patient was transferred to another hospital for terminal care. A computed tomography scan of the chest performed on (b) (6) revealed extensive mediastinal and hilar lymphadenopathy, hepatic metastasis, right rib destruction with associated soft tissue mass and increased attenuation in the soft tissues close to posterior elements in one of the lower dorsal vertebral bodies. That same day, the patient had a chest x-ray that revealed bilateral pulmonary opacities, fluid and probable pulmonary nodules; pneumonia and metastatic disease were considered likely. The patient's condition continued to deteriorate, and he was subsequently transferred to hospice care on (b) (6) with a final diagnosis of metastatic cancer of the esophagus. This patient took his last study drug dose on 19 Jul 2007 and discontinued from the study on 20 Jul 2007. He discontinued from the study because of vomiting. On (b) (6) the patient died from cancer of the esophagus with bone, liver and lung metastasis with hypercalcemia and renal failure. A death certificate was not provided; it is not known if an autopsy was performed. The investigator considered the vomiting possibly related to study drug. The investigator considered the esophageal cancer metastatic related to cancer of the esophagus, bone/liver metastasis with hypercalcemia and renal failure and not related to study drug. The medical monitor considered the esophageal cancer metastatic related to the fatal outcome and not related to study drug.

Since death in this patient occurred (b) (6) after the last dose of study medication, the cause of death did not appear to be related to study drug, and, in concurrence with the investigator's assessment, vomiting may have been related to study drug, while metastatic esophageal cancer, hypercalcemia and renal failure were likely related to the underlying disease.

Patient No.: 718701
Case No(s).: 2006EO000003
Event(s): Metastatic renal cell carcinoma; supraventricular tachycardia
Event Category(ies): Death; SAE
Relationship(s) to Study Drug: Not related
This 81-year-old male took EN3267 as needed starting on 02 Mar 2006 for episodes of breakthrough cancer pain and was taking 800 mcg sublingual tablets during the open-label titration phase of the study. The patient's medical history included dehydration, tonsillectomy, pleural effusions, hypertension, colon resection, appendectomy, diabetes, right nephroureterectomy, transurethral resection of prostate, marked fatigue with no focality, +1 edema of bilateral lower extremities, right hip replacement, supraclavicular mass, allergies to pollen and tape, and cancer-related pain. The patient's concomitant

medications included amlodipine, bisacodyl, fentanyl, guaifenesin, hydrocodone and acetaminophen, oxycodone, prochlorperazine, quinapril and rosiglitazone. On (b) (6) the patient was hospitalized for severe supraventricular tachycardia and metastatic renal cell carcinoma. The patient presented with diaphoresis and a history of experiencing a sensation of rapid abdominal fullness and swallowing difficulties resulting in minimal oral intake in the preceding few weeks. The patient took his last study drug dose on 03 Mar 2006 and discontinued from the study on the same day. The patient discontinued because of lack of efficacy. On (b) (6) a chest computed tomography revealed extensive metastases involving the mediastinum, liver, and left supraclavicular fossa and large pleural effusions. An echocardiogram revealed an ejection fraction of 69%, mild atrial enlargement and mild left ventricular hypertrophy. On (b) (6) the supraventricular tachycardia resolved, and the patient was transferred to an in-patient hospice unit. On (b) (6) the patient died because of the metastatic renal cell carcinoma. No autopsy was performed, and death certificate information was not provided. The investigator considered the metastatic renal cell carcinoma and supraventricular tachycardia related to the patient's concurrent illness and not related to study drug.

Since death in this patient occurred (b) (6) after the last dose of study medication, the investigator's determination that death in this patient was unrelated to study drug, and that supraventricular tachycardia and renal cell carcinoma were associated with the patient's concurrent illness are acceptable.

Patient No.: 746701
Case No(s).: 2006EO000019
Event(s): Breast cancer metastatic; cardiorespiratory arrest; dyspnea exacerbated
Event Category(ies): Death; SAE; discontinuation due to an AE
Relationship(s) to Study Drug: Not related
This 49-year-old female took EN3267 as needed starting on 24 Aug 2006 for episodes of breakthrough cancer pain and was taking 100 mcg sublingual tablets during the open-label titration phase of the study. She was not taking study drug at the time of the events. The patient's medical history included subcutaneous nodule left chest (<1 cm), decreased breath sounds at right hemithorax, persistent cough, pleural effusion, syncope secondary to vasovagal reaction, anorexia, nausea, reflux, hypoalbuminemia, hypokalemia, brain metastasis, paresthesias, intermittent swelling to right upper extremity (lymphedema), bone metastasis (sacroiliac joint spine), weakness in left hip, right hip cancer-related pain, right lateral costal rib cancer-related pain, liver lesions, anemia and modified radical right breast mastectomy. The patient's concomitant medications included acetaminophen, albumin, albuterol, alprazolam, darbepoetin alfa, dextrose and dopamine, dolasetron, epinephrine, furosemide, gemcitabine, imipenem and cilastatin, lorazepam, megestrol, methylprednisolone, omeprazole, oxycodone, pantoprazole, potassium chloride, sodium chloride and temazepam. The patient experienced mild dyspnea beginning 24 Aug 2006, and on 29 Aug 2006 her dyspnea exacerbated. The severe exacerbated dyspnea resolved on 30 Aug 2006, and study

drug was permanently discontinued on 31 Aug 2006 because of the exacerbation. On (b) (4) the patient experienced progressive shortness of breath and chest pain. A chest x-ray revealed a worsening of the right pleural effusion, with diffused metastases, and a computed tomography (CT) scan revealed small bilateral pleural effusions, pulmonary metastatic disease suspicious for lymphangitic carcinomatosis and diffuse osseous and hepatic metastases. The patient was hospitalized with a diagnosis of metastatic breast cancer. An echocardiogram performed that same day showed the patient was in sinus tachycardia with left atrial enlargement. An electroencephalogram revealed a suppression pattern consistent with severe cerebral dysfunction. On (b) (6) the patient was found not breathing and unresponsive. Resuscitation measures for cardiorespiratory arrest were successful, and the patient was placed on a ventilator. A CT scan of the brain revealed a prior infarction in the distribution of the posterior limb of the right middle cerebral artery, as well as findings consistent with a midline dermoid in the regions of the septum pellucidum extending into the region of the right thalamus. Neurology consultation findings suggested that the patient had a very poor prognosis due to anoxia and severe ischemic encephalopathy. The patient remained ventilated and unresponsive. Her family opted to have the ventilator withdrawn, and on (b) (6) the patient died, and the event of cardiorespiratory arrest was considered resolved. This patient took her last study drug dose on 31 Aug 2006 and discontinued from the study on 06 Sep 2006. She discontinued from the study because of the exacerbated dyspnea. On (b) (6) the patient died from metastatic breast cancer. An autopsy was not performed. The death certificate noted the patient's immediate cause of death was breast cancer. The investigator considered the AE of exacerbated dyspnea not related to study drug and the SAEs of metastatic breast cancer and cardiorespiratory arrest related to concurrent illness and not related to study drug. The medical monitor considered the metastatic breast cancer related to the underlying breast cancer with metastasis to the brain and pulmonary disease and not related to study drug and the cardiorespiratory arrest related to concurrent illness and not related to study drug.

The assessment by the medical monitor and investigator that the cause of death in this patient was unrelated to study medication is acceptable since the patient died (b) (6) after her last dose of ABSTRAL. Although dyspnea could be associated with study medication, the presence of pleural effusion and severe dyspnea (b) (4) after the last dose are not suggestive of a causal relationship to study medication.

Patient No.: 749704
Case No(s).: 2007EO000031
Event(s): Metastatic carcinoma of the bladder; prostate cancer metastatic
Event Category(ies): Death; SAE; discontinuation due to AE
Relationship(s) to Study Drug: Not related
This 76-year-old male took EN3267 as needed starting on 24 May 2007 for episodes of breakthrough cancer pain and was taking 800 mcg sublingual tablets during the open-label titration phase of the study. The patient's medical history included reactive airway

disease, benign essential hypertension, coronary atherosclerosis, edema, deep vein thrombosis, gastroesophageal reflux disease, intermittent diarrhea and nausea, decreased appetite, diabetes mellitus, hypercholesterolemia, acute renal failure, prostate and bladder cancer, anemia in neoplastic disease, arthritis and cancer-related pain. The patient's concomitant medications included diphenoxylate and atropine, esomeprazole, formoterol, furosemide, gemfibrozil, glipizide, levofloxacin, lorazepam, megestrol, morphine, oxycodone, pravastatin, prochlorperazine, rosiglitazone and warfarin. On 30 May 2007 the patient experienced progression of metastatic prostate and bladder cancer. The patient presented to the site on that day with 3+ pitting edema of the abdomen and lower extremities from the waist down, and distention of the abdomen with ascites present and a urinary tract infection. The SAEs were considered to be of severe intensity. The patient expressed dissatisfaction with study drug treatment because of a lack of pain relief. Study drug was discontinued, and the patient was referred to hospice. This patient took his last study drug dose on 28 May 2007 and discontinued from the study on 30 May 2007. He discontinued from the study because of progression of metastatic prostate and bladder cancer. On (b) (6) the patient died because of progression of metastatic prostate and bladder cancer. An autopsy was not performed, and the death certificate noted the cause of death as bladder cancer and prostate cancer. The investigator considered the SAEs related to concurrent illness and not related to study drug. The medical monitor considered the SAEs related to the patient's underlying metastatic cancer and not related to study drug.

Although there is inadequate data available to determine the cause death in this subject, it was unlikely to be related to study drug administration since his last dose was (b) (6) prior.

Death Due to Suicide

An additional death, completed suicide, was reported three days after the last dose of study drug administration in a patient with a history of depression and who was currently receiving antidepressants. The investigator and study monitor felt that this death was unrelated to study drug administration. Contribution of the study medication in the presence of background opioid use and a history of depression make it difficult to assign causality to worsening depression related to study medication administration. This case narrative is presented as follows:

Patient No.: 539510
Case No(s).: 2008EO000001; 2007EO000042
Event(s) Completed suicide; lobar pneumonia; suicide attempt (Received as 2 SAE reports)
Event Category(ies) Death; SAE; discontinuation due to an AE
Relationship(s) to Study Drug Not related
This 58-year-old female took EN3267 as needed starting on 19 Apr 2007 for episodes of breakthrough cancer pain and was taking 400 µg sublingual tablets during the long-

term extension phase of the study. The patient's medical history included cataracts, scalp dermatitis, eczema, right thoracotomy scar, rosacea, dry eyes, anthracosis, bronchitis, lung right non-small cell carcinoma Pancoast's tumor, pulmonary emphysema, right lung lobectomy with en bloc chest wall resection, right thoracotomy, acid reflux, constipation, diarrhea, diverticulitis, heartburn, hiatal hernia, nausea, frequent bladder infections, genital herpes, hysterectomy, surgically-induced menopause, thoracic lymphadenectomy, arthritis, cancer-related chest pain, cancer right upper quadrant pain/shoulder, cervical fusion C2 and C3, chest wall reconstruction, degenerative cervical disc disease, facet arthropathy, joint replacement/toe, lower extremity bilateral edema, numerous foot surgeries, right rib resection, right shoulder ligamental tear, 2 suicide attempts in 1985 and 1998, sciatica, spinal stenosis, allergies to razodone, iodine, esomeprazole, penicillin, lansoprazole, carisoprodol, sulfa, ranitidine, and anxiety, depression and insomnia. The patient's concomitant medications included acetylsalicylic acid, acyclovir, aluminum hydroxide and magnesium hydroxide, ascorbic acid, betamethasone valerate, bismuth subsalicylate, bupivacaine, calcium carbonate, clonazepam, conjugated estrogens, docusate and senna, duloxetine, erlotinib, etodolac, fentanyl, furosemide, gabapentin, hydrocodone and acetaminophen, hydrocortisone, hydromorphone, hydroxyzine, ibuprofen, iohexol, levofloxacin, lubiprostone, methylprednisolone, metronidazole, midazolam, modafinil, morphine, multivitamins, nitrofurantoin, olanzapine, oxycodone, promethazine, sertraline, sodium chloride, therapeutic radiopharmaceuticals, tizanidine, vancomycin and zolpidem. On (b) (6) the patient presented to the emergency room with complaints of worsening chest and back pain, shoulder pain and moderate exacerbated dyspnea. A chest x-ray revealed right middle lobe pneumonia. On the same day, the patient was hospitalized for severe lobar pneumonia. The patient was treated with vancomycin, levofloxacin and intravenous fluids for the pneumonia. On (b) (6) the lobar pneumonia resolved with sequelae of shortness of breath, and the patient was discharged from hospital. On (b) (6) the patient committed suicide by shooting herself in the head with a firearm. The patient took her last study drug dose on 17 Dec 2007. The investigator and medical monitor did not consider either the lobar pneumonia or the suicide to be related to study drug, but related to the patient's concurrent illness and underlying comorbid disease.

A summary of TEAEs associated with death for patients enrolled in the Phase 3 Studies are presented in Table 16 and Table 17 below.

Table 16: Summary of Treatment-Emergent Adverse Events Causing Death in Multiple-dose Cancer Patients by Pooled Dose Group

System Organ Class Preferred Term	Pooled Dose Group <=200 mcg (N=45) n (%)	>200 - ≤400 mcg (N=98) n (%)	>400 mcg (N=152) n (%)	Overall (N=270) n (%)
At least one TEAE resulting in death	4 (8.9)	8 (8.2)	17 (11.2)	29 (10.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (6.7)	5 (5.1)	13 (8.6)	21 (7.8)
Prostate cancer metastatic	1 (2.2)	2 (2.0)	3 (2.0)	6 (2.2)
Breast cancer metastatic	1 (2.2)	1 (1.0)	1 (0.7)	3 (1.1)
Colon cancer metastatic	1 (2.2)	0	1 (0.7)	2 (0.7)
Lung cancer metastatic	0	0	2 (1.3)	2 (0.7)
Metastatic renal cell carcinoma	0	0	2 (1.3)	2 (0.7)
Non-small cell lung cancer metastatic	0	0	2 (1.3)	2 (0.7)
Oesophageal cancer metastatic	0	1 (1.0)	1 (0.7)	2 (0.7)
Metastatic carcinoma of the bladder	0	0	1 (0.7)	1 (0.4)
Metastatic gastric cancer	0	0	1 (0.7)	1 (0.4)
Renal cancer metastatic	0	1 (1.0)	0	1 (0.4)
Infections and infestations	1 (2.2)	1 (1.0)	2 (1.3)	4 (1.5)
Pneumonia	0	1 (1.0)	0	1 (0.4)
Pneumonia herpes viral	0	0	1 (0.7)	1 (0.4)
Sepsis	0	0	1 (0.7)	1 (0.4)
Septic shock	1 (2.2)	0	0	1 (0.4)
Gastrointestinal disorders	0	1 (1.0)	1 (0.7)	2 (0.7)
Intestinal obstruction	0	0	1 (0.7)	1 (0.4)
Small intestinal obstruction	0	1 (1.0)	0	1 (0.4)

Cardiac disorders	0	1 (1.0)	0	1 (0.4)
Myocardial infarction	0	1 (1.0)	0	1 (0.4)
Psychiatric disorders	0	0	1 (0.7)	1 (0.4)
Completed suicide	0	0	1 (0.7)	1 (0.4)
Renal and urinary disorders	0	1 (1.0)	0	1 (0.4)
Azotaemia	0	1 (1.0)	0	1 (0.4)

Source: Integrated Summary of Safety, Table 11.5.1, P. 2997 of 4367.

Table 17: Summary of Treatment-Emergent Adverse Events Causing Death in Study EN3267-005 (All Treated Patients) by Study Phase

	Open-label Titration Phase (N=131)	Double-blind Treatment Phase (N=66)	Long-term Extension Phase (N=72)	Overall (N=131)
	n (%)	n (%)	n (%)	n (%)
Number of patients who died	2 (1.5)	0	8 (11.1)	10 (7.6)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (1.5)	0	4 (5.6)	6 (4.6)
Breast cancer metastatic	0	0	1 (1.4)	1 (0.8)
Lung cancer metastatic	0	0	1 (1.4)	1 (0.8)
Non–small cell lung cancer metastatic	1 (0.8)	0	0	1 (0.8)
Esophageal cancer metastatic	1 (0.8)	0	0	1 (0.8)
Prostate cancer metastatic	0	0	1 (1.4)	1 (0.8)
Renal cancer metastatic	0	0	1 (1.4)	1 (0.8)
Infections and infestations	0	0	2 (2.8)	2 (1.5)
Pneumonia	0	0	1 (1.4)	1 (0.8)
Septic shock	0	0	1 (1.4)	1 (0.8)
Cardiac disorders	0	0	1 (1.4)	1 (0.8)
Myocardial infarction	0	0	1 (1.4)	1 (0.8)
Psychiatric disorders	0	0	1 (1.4)	1 (0.8)
Completed suicide	0	0	1 (1.4)	1 (0.8)

Source: Clinical Study Report (EN3267-005), Table 52, P. 764 of 932.

7.3.2 Nonfatal Serious Adverse Events

All SAEs that did not result in death were assessed by reviewing the CRFs, narratives, and datasets provided by the Applicant. There were a total of 73 patients who experienced an SAE that did not result in death during the development program, including one subject in the multiple-dose healthy subject studies, two patients in the single-dose studies in cancer patients, and 70 patients in the multiple-dose studies in cancer patients. Most SAEs were classified (according to system organ class) as neoplasms benign, malignant and unspecified, or infections and infestations. As adjudicated by this review, none of the SAEs were definitely due to the administration of study drug. The Applicant reported two non-fatal SAEs, vomiting in a subject in a multiple-dose healthy subject study, and affect lability in a patient in a multiple-dose cancer patient study, that were considered to be probably related to study medication. However, the clinical status of these patients make it difficult to adequate assess causality. The majority of SAEs were reported as due to the patients underlying malignancies, progression, and complications of underlying malignancy. Due to the large number of SAEs (which is an expected finding given the patient population), this review does not contain a narrative summary for each patient who experienced an SAE. Instead, a tabular summary of all SAEs by population (healthy subjects vs. cancer patients), dose (single vs. multiple-dose; 100-800 mcg vs. pooled dose), and study phase (open-label titration vs. double-blind treatment vs. open-label extension) study phases (EN3267-007) may be found in the Appendices (9.4 Summary Tables of Nonfatal Serious Adverse Events).

In summary, none of the SAEs could definitely be attributed to the use of ABSTRAL. While some of these SAEs could reasonably be attributed to study drug, the events were found to be consistent with the patients' malignancies, treatments, concomitant medications, or other events surrounding the SAEs. No obvious associations with dose or study phase were noted.

Additional SAEs were reported in the 180-day safety update. Details may be found in section 8 of this review.

7.3.3 Dropouts and/or Discontinuations

A total of 67 patients from studies EN3267-005 and EN3267-007 discontinued study medication due to AEs, of which 66 withdrew from study prematurely. For 19 patients, the AE that led to discontinuation was reported as cancer progression. The following AEs, that were reported in more than one patient, resulted in discontinuation of study medication: nausea (n=7); somnolence (N=4); vomiting (n=3) and dyspnea (n=3); headache (n=2), pneumonia (n=2); and fatigue (n=2). Events leading discontinuation of

study medication occurred primarily during the open-label titration phase (n=32 patients), while 34 patients discontinued therapy during the open-label maintenance phase, and only one patient withdrew during the double-blind study phase. A dose-response associated with event occurrence was not observed. Additionally, 31 related AEs (n=27 subjects) resulted in study medication discontinuation, which occurred more frequently during the open-label titration phase.

In study EN3267-005, a total of 21 subjects withdrew consent. Ten subjects discontinued study during the open-label titration phase, 2 during the double-blind treatment phase, and 9 during the open-label maintenance phase. The reason subjects discontinued study could not be adjudicated for 8 of 10 patients in the open-label titration phase and one of two subjects in the blinded treatment phase. The narratives of these 12 patients are presented in the Appendices (9.5 Narratives of Subjects Who Withdrew Consent).

7.3.4 Significant Adverse Events

Significant opioid-related adverse events that led to dropout from the clinical trials include nausea, vomiting, dizziness, headache, and sedation. These events would be expected in this study population, either because of background opioid medications or the study drug.

Cardio-respiratory Adverse Events

The cardio-respiratory AEs associated with potent opioids and occurring in ≥ one patient from the Phase 3 multiple-dose cancer studies included:

- Bradycardia (n=5)
- Hypotension, including orthostasis (n=10)
- Hypoxia (n=2)
- Hypertension (n=5)
- Respiratory failure (n=3)

Events were typically reported during the multiple-dose open-label maintenance study phase. Higher incidences of cardio-respiratory AEs were observed in patients treated in the higher pooled dose groups, but this dose-response relationship may reflect a longer duration of exposure, and except for a case of bradycardia, events were not considered by the investigators to be related to study medication. Respiratory depression also was observed in 12 healthy subjects who received 800 mcg as a single dose without naltrexone pretreatment, with one subject experiencing syspnea.

Hepatic Adverse Events

No hepatic events were observed in healthy subjects participating in the multiple-dose studies or in cancer patients in the single-dose studies. In Study 2246-EU-001, one

healthy volunteer, who received 800 mcg of Abstral and was pretreated with naltrexone, experienced elevated liver enzymes on study day 39, which resolved by study day 52. The event was considered possibly related to study medication by the investigator, and was rated as mild in severity. A second healthy volunteer who received 200 mcg of Abstral without naltrexone pretreatment experienced elevated alanine aminotransferase serum concentrations on study day 38. The investigator reported the event as possibly related to study medication and rated the severity as mild.

A total of 25 hepatic disorder events were observed (Table 18) in the multiple-dose cancer patient population. No trends were observed that suggested a dose-response relationship, and none of these were considered related to study medication by the investigators.

Table 18: Summary Table of Hepatic Disorder Events in the Multiple-dose Studies in Cancer Patients

Event	Reported as Treatment-Related	Severity
Ascites (n=7)	7 Not related	6 Moderate/1 severe
Inc. Alkaline phosphatase (n=4)	3 Not related 1 Unlikely related	2 Mild/1 moderate/1 severe
Jaundice (n=2; 3 events)	Not related	3 Mild
Hepatomegaly (n=2)	2 Not related	1 Mild/1 moderate
Abnormal liver function test (n=2)	1 Not related 1 Unlikely related	1 Mild/1 moderate
Inc. hepatic enzyme (n=1; 2 events)	2 Not related	2 Mild
Hepatic cirrhosis (n=1)	Not related	Moderate
Hepatic lesion (n=1)	Not related	Mild
Hepatic cyst (n=1)	Not related	Mild
Hepatic cancer metastatic (n=1)	Not related	Severe
Hepatitis (n=1)	Not related	Moderate

Source: Modified from Summary of Clinical Safety, page 46 of 74.

7.3.5 Submission Specific Primary Safety Concerns

Adverse Events Involving the Mouth

Oral tolerability and presence of abnormal mucosa were assessed in several of the healthy volunteers studies (2246-EU trials). In the multiple-dose Phase 3 BTcP studies (EN3267-005 and EN3267-007), at each visit, subjects were assessed for evidence of mucositis, oral ulcers and the presence and severity of erythema. In the healthy volunteer studies, oral mucosal AEs were reported in 4% (n=9) of subjects in the single dose studies with naltrexone pretreatment and 4.8% (n=7) of subjects without naltrexone pretreatment. The cumulative rate of oral mucosal AEs was 24% in the Phase 3 cancer patient populations. The majority of these AEs were not attributed to the use of the study medication and were recorded during the multiple-dose open-label maintenance phase of study EN3267-007. One case of an application site reaction in a healthy subject was attributed to the study medication. There did not appear to be a gender, age or dose response relationship between study medication and the occurrence of oral mucosal AEs. Symptom severity was typically reported as mild and self-limited.

The following AEs were reported in at more than one subject in the multiple-dose BTcP studies: stomatitis (n=20); dry mouth (n=11); oropharyngeal pain (n=8); tooth infection (n=4), lip ulceration (n=4), and mouth ulceration (n=4); cheilitis (n=3); dental caries (n=3); oropharyngeal candidiasis (n=3); gingivitis (n=2); tongue ulceration (n=2); herpes simplex (n=2); oral candidiasis (n=2); pharyngitis (n=2); streptococcal pharyngitis (n=2); tooth abscess (n=2); and mucosal inflammation (n=2).

A summary of the local treatment-emergent AEs with ABSTRAL reported for EN3267-005 by study phase is as follows:

Open-label titration (n=131):
Stomatitis 1 (0.8%)
Mucositis 6 (5%)
Mucosal blistering 1 (0.8%; mild in intensity and considered not related to study medication)

Double-blind treatment phase (n=66):
Stomatitis 3 (4.5%)
Mucositis 3 (4.5%)
Mucosal blistering 1 (1.5%; mild in intensity and considered not related to study medication)

Long-term extension (n=72):
Stomatitis 7 (9.7%)
Mucositis (1 patient reporting mucositis at end of study visit #18)

Summary tables characterizing the occurrence of AEs involving the mouth by population (healthy volunteers vs. cancer), drug exposure (single-dose vs. multiple dose), and study phase (open-label titration vs. double-blinded treatment vs. open-label maintenance) are presented in the Appendices (9.6 Summary Tables of Adverse Events of the Mouth). The incidences of occurrence did not appear to be associated with dose, but, as anticipated, many of the AEs occurred during the long-term open-label study phases. The adverse events related to the oral cavity appear most consistent with advanced cancer (stomatitis and mucositis). While a small number of these events may be related to the dosage form, the incidence is very low and the events were mild and self-limited.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly observed adverse reactions among the 270 opioid-tolerant cancer patients treated with ABSTRAL in the long-term multiple-dose Phase 3 studies included typical opioid adverse reactions, such as nausea, constipation, somnolence and headache. Since the Phase 3 clinical trials were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain, all patients were taking concomitant opioids, which may have contributed to these findings. Common TEAEs observed in ≥ 5% of patients by pooled dose group are presented in Table 19. Of 27 TEAEs reported in these studies, nausea (22.6% of patients), vomiting (12.2%), and fatigue (11.9%) occurred most frequently, with higher incidences of upper respiratory tract infection, urinary tract infection, headache, cancer pain, dehydration, anorexia, and anemia reported in the higher dose groups. Based on system organ class, gastrointestinal disorders (occurring in approximately 46% of subjects) were most commonly reported. The Applicant also summarized common AEs by study phase and individual dose group in the multiple-dose studies for the Open-label Titration Phase (Table 20) and for the Open-label Maintenance Phase (Table 21). Only nausea (8.9%) and somnolence (5.2%) were reported at a frequency of more than 5% during the titration phase, while during the maintenance phase, nausea, vomiting, fatigue, edema peripheral, stomatitis, back pain, and dehydration were each reported in ≥ 10% of patients. No dose response or time-dependency for AE occurrence was reported or noted.

Table 19: Summary of Common TEAEs (Reported in ≥ 5% of Subjects) by Pooled Dose Group – Multiple-dose Studies in Cancer Patients

System Organ Class Preferred Term	Pooled Dose Group			
	≤ 200 µg (N=45)	> 200 to ≤ 400 mcg (N=98)	> 400 µg (N=152)	Overall (N=270)
	n (%)	n (%)	n (%)	n (%)
At least 1 TEAE in at least 5% of patients	**25 (55.6)**	**56 (57.1)**	**97 (63.8)**	**167 (61.9)**
Gastrointestinal disorders	**17 (37.8)**	**47 (48.0)**	**67 (44.1)**	**125 (46.3)**
Nausea	10 (22.2)	20 (20.4)	31 (20.4)	61 (22.6)
Vomiting	3 (6.7)	12 (12.2)	18 (11.8)	33 (12.2)
Stomatitis	3 (6.7)	6 (6.1)	11 (7.2)	20 (7.4)
Diarrhoea	2 (4.4)	8 (8.2)	9 (5.9)	19 (7.0)
Constipation	1 (2.2)	7 (7.1)	10 (6.6)	18 (6.7)
Dry mouth	1 (2.2)	5 (5.1)	5 (3.3)	11 (4.1)
Infections and infestations	**9 (20.0)**	**19 (19.4)**	**64 (42.1)**	**91 (33.7)**
Upper respiratory tract infection	0	1 (1.0)	12 (7.9)	13 (4.8)
Urinary tract infection	1 (2.2)	2 (2.0)	9 (5.9)	12 (4.4)
Nervous system disorders	**9 (20.0)**	**25 (25.5)**	**57 (37.5)**	**88 (32.6)**
Somnolence	2 (4.4)	8 (8.2)	9 (5.9)	19 (7.0)
Dizziness	3 (6.7)	9 (9.2)	6 (3.9)	18 (6.7)
Headache	1 (2.2)	5 (5.1)	12 (7.9)	17 (6.3)
General disorders and administration site conditions	**16 (35.6)**	**20 (20.4)**	**55 (36.2)**	**87 (32.2)**
Fatigue	5 (11.1)	10 (10.2)	18 (11.8)	32 (11.9)
Oedema peripheral	3 (6.7)	4 (4.1)	15 (9.9)	21 (7.8)
Asthenia	4 (8.9)	3 (3.1)	12 (7.9)	19 (7.0)
Musculoskeletal and connective tissue disorders	**9 (20.0)**	**17 (17.3)**	**40 (26.3)**	**64 (23.7)**
Back pain	3 (6.7)	3 (3.01	12 (7.9)	18 (6.7)
Arthralgia	2 (4.4)	4 (4.1)	11 (7.2)	17 (6.3)
Pain in extremity	3 (6.7)	4 (4.1)	7 (4.6)	13 (4.8)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**7 (15.6)**	**10 (10.2)**	**43 (28.3)**	**60 (22.2)**
Cancer pain	1 (2.2)	1 (1.0)	13 (8.6)	15 (5.6)
Breast cancer metastatic	3 (6.7)	1 (1.0)	2 (1.3)	6 (2.2)
Respiratory, thoracic, and mediastinal disorders	**6 (13.3)**	**13 (13.3)**	**33 (21.7)**	**51 (18.9)**
Dyspnoea	2 (4.4)	4 (4.1)	10 (6.6)	16 (5.9)

Source: Integrated Summary of Safety, Table 2-7, P. 69-70 of 156.

Table 19. Cont.

System Organ Class Preferred Term	Pooled Dose Group			
	≤ 200 µg (N=45)	> 200 to ≤ 400 mcg (N=98)	> 400 µg (N=152)	Overall (N=270)
	n (%)	n (%)	n (%)	n (%)
Skin and subcutaneous tissue disorders	**8 (17.8)**	**11 (11.2)**	**32 (21.1)**	**51 (18.9)**
Rash	1 (2.2)	2 (2.0)	8 (5.3)	11 (4.1)
Psychiatric disorders	**8 (17.8)**	**11 (11.2)**	**29 (19.1)**	**47 (17.4)**
Insomnia	3 (6.7)	1 (1.0)	14 (9.2)	18 (6.7)
Anxiety	4 (8.9)	1 (1.0)	9 (5.9)	14 (5.2)
Investigations	**2 (4.4)**	**12 (12.2)**	**32 (21.1)**	**46 (17.0)**
Weight decreased	1 (2.2)	7 (7.1)	8 (5.3)	16 (5.9)
Metabolism and nutrition disorders	**2 (4.4)**	**13 (13.3)**	**30 (19.7)**	**45 (16.7)**
Dehydration	1 (2.2)	6 (6.1)	12 (7.9)	19 (7.0)
Anorexia	1 (2.2)	4 (4.1)	10 (6.6)	15 (5.6)
Blood and lymphatic system disorders	**8 (17.8)**	**10 (10.2)**	**26 (17.1)**	**42 (15.6)**
Anemia	2 (4.4)	6 (6.1)	11 (7.2)	19 (7.0)

Source: Integrated Summary of Safety, Table 2-7, P. 69-70 of 156.

Table 20: Adverse Reactions Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class Preferred term N (%)	100 mcg (n=22)	200 mcg (n=23)	300 mcg (n=55)	400 mcg (n=38)	600 mcg (n=52)	800 mcg (n=80)	Total (n=270)
Gastrointestinal disorders							
Nausea	1 (4.5)	4 (17.4)	5 (9.1)	1 (2.6)	2 (3.8)	2 (2.5)	15 (5.6)
Nervous system disorders							
Somnolence	0	2 (8.7)	4 (7.3)	2 (5.3)	2 (3.8)	2 (2.5)	12 (4.4)
Dizziness	0	0	3 (5.5)	2 (5.3)	0	1 (1.3)	6 (2.2)
Headache	0	0	0	1 (2.6)	3 (5.8)	1 (1.3)	5 (1.9)

Source: Integrated Summary of Safety, Table 2-12, P. 81 of 156.

Table 21: Adverse Reactions Which Occurred During Maintenance Therapy at a Frequency of ≥ 5%

System Organ Class Preferred term N (%)	100 mcg (n=7)	200 mcg (n=12)	300 mcg (n=22)	400 mcg (n=20)	600 mcg (n=35)	800 mcg (n=72)	Total (n=168)
Gastrointestinal disorders							
Nausea	1 (14.3)	0	2 (9.1)	0	1 (2.9)	6 (8.3)	10 (6.0)
Stomatitis	0	1 (8.3)	1 (4.5)	0	0	1 (1.4)	3 (1.8)
Constipation	0	0	1 (4.5)	2 (10.0)	1 (2.9)	4 (5.6)	8 (4.8)
Dry mouth	0	0	0	1 (5.0)	2 (5.7)	0	3 (1.8)
Nervous system disorders							
Headache	0	0	0	2 (10.0)	1 (2.9)	2 (2.8)	5 (3.0)
Dysgeusia	1 (14.3)	0	0	0	0	1 (1.4)	2 (1.2)
General disorders and administration site conditions							
Fatigue	0	0	0	1 (5.0)	2 (5.7)	0	3 (1.8)
Injury, poisoning and procedural complications							
Accidental overdose	1 (14.3)	0	0	0	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	0	1 (8.3)	0	0	0	0	1 (0.6)
Skin and subcutaneous disorders							
Hyperhidrosis	1 (14.3)	0	0	0	0	1 (1.4)	2 (1.2)

Source: Integrated Summary of Safety, Table 2-13, P. 81 of 156.

The frequencies of AEs listed below represent the ≥ 1% of patients from the open-label and double-blind phase 3 studies who experienced that reaction while receiving ABSTRAL.

Adverse Events (≥ 1%)

- *Cardiac disorders:* bradycardia, tachycardia
- *Eye disorders:* vision blurred
- *Gastrointestinal disorders:* abdominal pain, abdominal pain upper, constipation, dry mouth, dyspepsia, gingival ulceration, impaired gastric emptying, lip ulceration, mouth ulceration, nausea, stomach discomfort, stomatitis, tongue disorder, vomiting
- *General disorders and administration site conditions:* asthenia, drug withdrawal syndrome, fatigue, malaise
- *Immune system disorders:* drug hypersensitivity
- *Injury, poisoning and procedural complications:* accidental overdose

- *Metabolism and nutrition disorders:* anorexia, decreased appetite
- *Nervous system disorders:* amnesia, disturbance in attention, dizziness, dysgeusia, headache, hypoaesthesia, lethargy, parosmia, somnolence, tremor
- *Psychiatric disorders:* affect lability, anxiety, confusional state, depression, disorientation, dysphoria, euphoric mood, insomnia, mental status changes, paranoia, sleep disorder
- *Reproductive system and breast disorders:* erectile dysfunction
- *Respiratory, thoracic and mediastinal disorder:* dyspnoea, oropharyngeal pain, throat tightness
- *Skin and subcutaneous disorders:* hyperhidrosis , night sweats, pruritis, rash, skin lesion
- *Vascular disorders:* hypotension

Source: Integrated Summary of Safety, End of text Table 9.6, P. 1337-1473 of 4367.

7.4.2 Laboratory Findings

Due to the known clinical laboratory safety of fentanyl, postdose assessment was performed in the open-label study (EN3267-007) only for patients in the multiple dose BTcP studies. Clinically significant changes in clinical laboratory results were observed in this cancer population with numerous comorbidities who were receiving potentially toxic concomitant therapies for their underlying disease. Given the lack of appropriate comparator data, the progression of disease, and the concomitant medications and therapies, these data are not interpretable.

7.4.3 Vital Signs

Mean and median values for all vital signs cancer patients in the multiple dose study were within acceptable ranges both at baseline and post study medication exposure (Table 22). However, vital signs were not assessed post-dose for study EN3267-005. Given the lack of appropriate comparator data, the progression of disease, and the concomitant medications and therapies, these data are not interpretable.

Table 22: Vital Signs Pre- and Post-Dose for Cancer Patients in the Multiple Dose Study

		Dose					
	Statistic	100 mcg (N=8)	200 mcg (N=12)	300 mcg (N=20)	400 mcg (N=19)	600 mcg (N=28)	800 mcg (N=52)
Respiratory Rate Pre-Dose	N	6	10	18	17	24	46
	Mean	18.7	17.6	16.4	16.2	16.8	17.1
	Std	1.63	2.27	3.11	2.31	2.88	2.53
	Median	19.0	18.0	17.0	16.0	17.0	16.0
	Minimum	16	12	10	12	10	13
	Maximum	20	20	22	20	20	24
Respiratory Rate Post-Dose	N	6	10	18	17	24	46
	Mean	17.5	18.8	16.1	15.9	16.8	17.1
	Std	2.17	3.55	4.09	2.11	2.23	2.61
	Median	17.0	18.0	18.0	16.0	17.0	16.0
	Minimum	15	12	8	11	10	13
	Maximum	20	26	22	20	20	28
Heart Rate Pre-Dose	N	6	11	19	18	26	47
	Mean	78.5	85.5	81.4	75.4	80.7	79.3
	Std	16.50	14.30	19.65	19.02	15.54	13.41
	Median	78.5	80.0	76.0	71.0	80.0	78.0
	Minimum	57	70	52	54	54	50
	Maximum	104	113	132	118	108	111
Heart Rate Post-Dose	N	6	11	19	18	26	47
	Mean	85.5	94.9	86.9	76.7	84.4	84.2
	Std	20.61	15.51	22.04	15.80	16.11	15.66
	Median	76.0	90.0	84.0	72.5	80.5	81.0
	Minimum	66	76	58	56	60	57
	Maximum	120	128	154	113	139	128
Systolic BP Pre-Dose	N	6	11	19	18	26	47
	Mean	134.2	121.9	126.9	120.8	122.7	123.6
	Std	23.74	17.96	17.20	17.92	18.60	14.07
	Median	128.5	122.0	128.0	113.0	117.0	122.0
	Minimum	110	89	98	94	90	96
	Maximum	178	154	178	159	176	162

Source: Integrated Summary of Safety, Tables 2.6, P. 4050-1 of 4367.
Vitals for study EN3267-005 are not included on this table because they were only collected pre-dose.

7.4.4 Electrocardiograms (ECGs)

Given the lack of appropriate comparator data, the progression of disease, and the concomitant medications and therapies, these data are not interpretable.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were submitted with this application.

7.4.6 Immunogenicity

This category is not applicable to this study drug.

7.5 Other Safety Explorations

No additional safety explorations were performed for this applicable.

7.5.1 Dose Dependency for Adverse Events

This is not applicable to this application.

7.5.2 Time Dependency for Adverse Events

This is not applicable to this application.

7.5.3 Drug-Demographic Interactions

This is not applicable to this application.

7.5.4 Drug-Disease Interactions

This is not applicable to this application.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not assessed during the clinical development of ABSTRAL. However, it is known that fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when fentanyl is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of fentanyl with any CYP3A4 inhibitor may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.

The concomitant use of fentanyl with potent CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, and troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

For this limited indication in patients with advanced malignancy, an assessment of carcinogenicity was not required.

7.6.2 Human Reproduction and Pregnancy Data

There is no data on human reproduction and pregnancy for this study drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

There was no assessment for the effect of ABSTRAL on growth.

The Applicant requested a partial waiver for children 2 years of age and less because it would be impractical to conduct an adequate and well-controlled trial based on the following factors:

- Limited number of children with BTcP in this age group
- Lack of validated pain assessment instruments in this subpopulation

Approved labeling for other fentanyl products include the following statements:

- **Actiq®** (fentanyl citrate oral transmucosal lozenge; reference listed drug): "Safety and efficacy in pediatric patients below the age of 16 years have not been established."
- **Duragesic®** (fentanyl transdermal system): "DURAGESIC was not studied in children less than 2 years of age. Duragesic should be administered to children only if they are opioid-tolerant and 2 years of age or older."
- **Fentora®** (fentanyl citrate oral transmucosal lozenge): "The safety and efficacy of FENTORA have not been established in pediatric patients below the age of 18 years"
- **Onsolis®** (fentanyl buccal soluble film): "Safety and efficacy in pediatric patients below the age of 18 years have not been established."
- **Sublimaze®** (fentanyl citrate injection): "The safety and efficacy of SUBLIMAZE in children under 2 years of age have not been established."

The Applicant requested a deferral of the Pediatric Assessment required under PREA because the NDA was ready for approval in adults. The Applicant submitted a Pediatric Development Plan to the Division on 29 July 2009. An open-label safety and pharmacokinetic trial in children and adolescents from 3 years to 16 years of age. Since efficacy can be extrapolated from adequate and well-controlled studies in adults, pediatric efficacy studies will not be necessary in this subpopulation.

The Division met with the Pediatric Research Committee (PeRC) on 3 February 2010 to review the Applicant's requests. PeRC concurred with the Applicant's proposal to conduct a pharmacokinetic and safety study, and did not have any additional questions or concerns at that time.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

During the clinical development program, a single patient (0561-0504) experienced an AE (mental confusion) reported as an accidental overdose while receiving a 100 µg dose of ABSTRAL on Study Day 161 during the open-label maintenance phase of Study EN3267-005. The suspect drugs included lorazepam, oxycodone, morphine, and study medication. This TEAE resolved, but was considered to be possibly related to study medication and rated as moderate in severity.

A second patient (0811-0701), also enrolled in the open-label phase of Study EN3267-005, was hospitalized on three occasions (over 7 months of therapy with ABSTRAL) for three separate events that included dehydration, hyponatremia, and myocardial ischemia. The hospitalization for hyponatremia was considered to be related to the metabolic effects of an overdose of analgesics. The patient was reinstructed on the proper use of pain medication, including study medication. Following further counseling regarding proper use of the study medication and analgesics, the patient was reinstituted on study medication and continued in the study without event recurrence.

7.7 Additional Submissions / Safety Issues

On 1 February 2010, the Applicant submitted a revised Risk Evaluation Minimization Strategy (REMS) for ABSTRAL to the Division. The revisions to the original REMS were extensive and included the following:

- Refined and clarified goals
- Added information on how the Medication Guide is supplied and details of where additional Medication Guides can be obtained
- Updated definition of prescribers and pharmacies
- Updated website function and role of call center
- Provided further details on educational materials for prescriber and pharmacy
- Updated enrollment criteria for prescriber, pharmacy, distributor, and patient
- Provided detail on substantive changes that require re-enrollment for prescriber, pharmacy, and distributor
- Updated list of forms for prescriber and pharmacy
- Provided detail on patient inactivation and number of prescribers allowed per patient
- Updated list of forms
- Clarified implementation system
- Added details on how pharmacies verify prescription eligibility
- Updated (b) (4) assessment plan

The updated REMS Supporting Documents included:

- Removed details on long acting opioids
- Updated risk tables
- Updated goals to reflect change in REMS document
- Included supporting information on proposed REMS Elements
- Added information on how the Medication Guide is supplied and details of where additional Medication Guides can be obtained
- Updated definition of prescribers and pharmacies
- Updated website function and role of call center
- Description of elements updated
- Clarified prescriber education and enrollment
- Provided detail on substantive changes that require re-enrollment
- Updated prescriber information that will be provided
- Clarified pharmacy education and enrollment
- Provided detail on substantive changes that require re-enrollment
- Updated pharmacy information that will be provided
- Clarified patient education and enrollment
- Provided detail on patient inactivation and number of prescribers
- Updated patient information that will be provided
- Details provided on methodology available for verifying prescription eligibility
- Update distributor enrollment details and responsibilities
- Clarified implementation system
- Added details on how pharmacies verify prescription eligibility
- Updated data sources
- Added details on the (b) (4) program steering committee
- Added details on the (b) (4) program operations team

On 16 February 2010, the Division held the first REMS meeting, during which the Risk Project Management Team reiterated their concerns with submission of an extensively revised REMS program at this late stage of the review period.

The three primary goals identified in the revised ABSTRAL REMS (b) (4) are to:

1. Ensure appropriate patient selection for ABSTRAL, which includes avoiding ABSTRAL use in opioid non-tolerant patients
2. Educate prescribers, pharmacists and patients on the proper dosing, administration, storage and disposal of ABSTRAL
3. Reduce the potential for misuse, abuse and diversion of ABSTRAL

The (b) (4) program includes the following key features:

1. Medication Guide

- The Medication Guide that will conform to the requirements of 21 CFR 208.24 is dispensed with each ABSTRAL prescription and included as an attachment to the (b) (4) introductory letters sent to each stakeholder.
- The Medication Guide will include information regarding risks associated with the use or misuse of ABSTRAL, precautions for safe use of the product, essential elements of the (b) (4) program, and contact information for customer assistance (i.e., call center with toll-free number and website).

2. Communication Plan
   - The Applicant will implement a communication plan to distributors, prescribers and pharmacies that will include the following:
     - Dear Prescriber Letters
     - Dear Pharmacist Letters
     - Dear Distributor Letters
     - The (b) (4) program website
     - The (b) (4) program call-centre
   - Communications will be accompanied by a copy of the approved prescribing information.
   - Additional materials will be available via the program website (b) (4) or through the (b) (4) program toll-free number (1-888-ABSTRAL).

3. Elements to Assure Safe Use (ETASU)
   - The key elements of this REMS that mitigate the risks associated with the use of ABSTRAL are as follows:
     a. ABSTRAL will only be prescribed by healthcare providers who are certified under 505-1(f)(3)(A).
        - Prescribers must complete the (b) (4) prescriber education materials and knowledge assessment of risks and appropriate use of ABSTRAL prior to certification including:
          - Risk of overdose caused by giving ABSTRAL to someone for whom it has not been prescribed
          - Risk of overdose due to prescribing ABSTRAL to opioid non-tolerant patients
          - Risks of inappropriately converting patients on a mcg per mcg basis from another fentanyl product to ABSTRAL
          - Risk of addiction from exposure to ABSTRAL and potential risks of misuse, diversion and abuse

     b. Pharmacies that dispense ABSTRAL will be certified under 505-1(f)(3)(B).
        - A responsible pharmacist for each pharmacy must complete the (b) (4) pharmacy education materials and knowledge assessment

regarding the risks of ABSTRAL dispensing and appropriate use of the product.

- Training regarding the risks associated with ABSTRAL (as described for the Prescriber above) is to be completed by all pharmacists who dispense ABSTRAL.
- Each patient is counseled by a trained pharmacist regarding the benefits and risks of ABSTRAL, and a Medication Guide will be provided with each prescription.

c. An enrolled drug distributor will only ship ABSTRAL to certified pharmacies and ensure the following:
   - Training of relevant staff on the (b) (4) program procedures
   - Shipping ABSTRAL only to those pharmacies whose enrollment has been validated
   - Providing data to the (b) (4) program including information on shipment to enrolled pharmacies
   - Cooperating with periodic audits or non-compliance investigations to ensure that ABSTRAL is distributed in accordance with the program requirements

d. Prior to being given an ABSTRAL prescription, each patient must be enrolled in the (b) (4) program with documentation of safe-use conditions under 505-1(f)(3)(D) as follows:
   - Prescriber
     - Counsel each patient enrolled in the (b) (4) program and reviewing the Medication Guide prior to the prescriber and patient (or authorized representative) signing the enrollment form
     - Acknowledge that the patient is opioid tolerance
     - Discuss the benefits and risks of ABSTRAL with the patient
     - Provide the patient with a medication guide
   - Patient
     - Receive a copy of the Medication Guide and review with prescriber
     - Discuss with prescriber any questions or concerns regarding ABSTRAL
     - Understand that there can be serious risks, which could be life threatening, especially if ABSTRAL is not taken as directed
     - Report any side effects or adverse events to prescriber
     - Regularly use another opioid pain medicine for background pain
     - Never give ABSTRAL to anyone else
     - Store ABSTRAL in a safe place away from children
     - Review the Patient Authorization for Disclosure and Use of Health Information Statement and authorize healthcare providers and health plans to disclose personal and medical information to ProStrakan or their agent.

4. Implementation System
   - The implementation system, based on 505-1(f)(3)(B) and 505-1(f)(3)(D), will include the following:
     - Maintaining a database of all enrolled prescribers, pharmacies, and patients
     - Monitoring distribution data and prescription data to ensure that only enrolled/certified distributors, pharmacies and prescribers are distributing, dispensing, and prescribing ABSTRAL
     - Verifying prescription eligibility by enrolled pharmacies prior to dispensing

5. Timetable for Submission of Assessments
   - The Applicant will submit, within the Periodic Reports, an assessment of the (b) (4) program to the Agency every 6 months for the first year following ABSTRAL launch, then annually thereafter that will minimally include:
     - Surveying healthcare providers understanding of the serious risks associated with ABSTRAL
     - Reporting on the status of the training and certification program for healthcare professionals
     - Evaluating the effectiveness of the REMS program through:
       a. A claims study to evaluate ABSTRAL utilization patterns including opioid-tolerant utilization patterns
       b. An analysis and summary of safety surveillance and monitoring activities for abuse, misuse, and overdose and any intervention taken resulting from signals of abuse, misuse, and overdose
     - Reporting failures to adhere to distribution, prescribing and dispensing requirements, and corrective actions taken to address noncompliance

In addition, ABSTRAL will be designated Schedule II under the federal CSA. The product will be subject to strict regulatory controls along its entire distribution pathway to ensure that access to the product is restricted in accordance with regulatory requirements. Because of the differences in bioavailability, care must be taken in prescribing transmucosal fentanyl products, and switching between them for the treatment of cancer-related breakthrough pain. ABSTRAL is supplied in six dosage strengths (100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg, and is available in child-resistant, protective blister cards with peelable foil. Each tablet is white in color, with the strength distinguishable by the shape of the dosage unit and by de-bossing on the tablet surface.

8 Postmarket Experience

As of October 2009, ABSTRAL is authorized in 23 countries (22 EU countries), and marketed in five (France, Germany, Greece, Sweden, and the United Kingdom). The product was first launched in Sweden in February 2008 and in the UK and Germany as of 1 July 2009. One new post-marketing registry has been initiated in the United Kingdom, and one post-marketing surveillance study is ongoing in Germany. Since first approved, post-marketing reports have been captured via Periodic Safety Update Reports (PSURs). At the time of the submission, the Applicant acknowledged that five case reports with six related AEs have been reported to ProStrakan, all of which were considered non-serious by the reporters. All of these AEs, except for one report of lack of efficacy, were expected for fentanyl. During the review period from 1 March 2009 through 31 August 2009, an additional 15 case reports (including eight SAEs [four deaths] and one non-serious unexpected event) associated with sublingual fentanyl use have been submitted to the Applicant. The deaths appeared to be attributed to disease progression and associated complications. However limited information was provided to adequately assess causality. All SAEs and non-serious unexpected events were reported as unrelated or unlikely related to ABSTRAL. Although two of the events (tongue swelling and opioid withdrawal syndrome; reported as resolving) could possibly be related to sublingual fentanyl administration, the limited information provided and the presence of background opioid use, make it difficult to adequately assess causality. No cases of pregnancy, overdose, or drug misuse, abuse or diversion were reported. Overall, no obvious or unexpected safety signals were noted.

The PSUR also includes routine assessment of the published literature for additional safety signals relevant to fentanyl use and postmarketing surveillance. The search tools utilized for literature searches include: AdisReactions, Medline, Biosis, Current Contents, Web of Science, conference proceedings, Excerpta Medica, Toxline and Derwent Drug file. None of the articles identified during the last review period refer to sublingual administration of fentanyl and the literature did not reveal any additional unexpected safety concerns or identify additional safety signals.

Only one additional SAE (reflux esophagitis and vomiting in a 64 y/o male considered possibly related to sublingual fentanyl that resolved with interruption of therapy) was reported by the applicant for the two previous 180-day time periods (from 1 September 2008 to 28 February 2009 and 29 February 2008 to 31 August 2008) covered under the PSUR.

Since first launched until 31 October 2009, the Applicant has received 19 case reports with 34 possible AEs. Most of the events were reported as non-serious, and expected with the use of a fentanyl product. A summary of these AEs is presented below ().

Table 23: Postmarketing Suspected Adverse Drug Reactions (18 August 2008 to 31 October 2009)

MedDRA PT	SOC	Number of Events
Dizziness	Nervous system disorders	5
Nausea	Gastrointestinal disorders	4
Fatigue	General disorders and administration site conditions	3
Drug ineffective	General disorders and administration site conditions	2
Swollen tongue	Gastrointestinal disorders	2
Vomiting	Gastrointestinal disorders	2
Anorexia	Metabolism and nutrition disorders	1
Asthenia	General disorders and administration site conditions	1
Drug withdrawal syndrome	General disorders and administration site conditions	1
Dyspnoea	Respiratory, thoracic and mediastinal disorders	1
Glossitis	Gastrointestinal disorders	1
Glossodynia	Gastrointestinal disorders	1
Heart rate increased	Investigations	1
Hyperhidrosis	Skin and subcutaneous tissue disorders	1
Oedema mouth	Gastrointestinal disorders	1
Oral pain	Gastrointestinal disorders	1
Overdose	Injury, poisoning and procedural complications	1
Palpitations	Cardiac disorders	1
Respiratory depression	Respiratory, thoracic and mediastinal disorders	1
Somnolence	Nervous system disorders	1
Stomatitis	Gastrointestinal disorders	1
Vision blurred	Eye disorders	1
Total		**34**

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Source: Amendment 0009, Table 1, P. 3 of 5.

9 Appendices

9.1 Literature Review/References

Literature is referenced throughout the review as needed.

9.2 Labeling Recommendations

There are three previously approved oral transmucosal fentanyls for breakthrough cancer pain. The proposed labeling was based on those labels. Because this product does not appear to have specific advantages or disadvantages compared to the other products (ABSTRAL is bioequivalent to Actiq), the ABSTRAL label should closely conform to those labels.

9.3 Advisory Committee Meeting

There is no advisory committee meeting planned for this application.

9.4 Summary Tables of Nonfatal Serious Adverse Events

Table 24: Serious Adverse Eavents Reported in the Multiple-dose Healthy Subject Studies

	Dose (1)					
System Organ Class Preferred Term	50 mcg (N=10) n (%)	100 mcg (N=21) n (%)	200 mcg (N=18) n (%)	300 mcg (N=6) n (%)	400 mcg (N=15) n (%)	800 mcg (N=12) n (%)
At least one serious TEAE	0	0	1 (5.6)	0	0	0
Gastrointestinal disorders	0	0	1 (5.6)	0	0	0
Vomiting	0	0	1 (5.6)	0	0	0

Source: Integrated Summary of Safety, Table 12.3, P. 3015 of 4367.

Table 25: Serious Adverse Events Reported in the Multiple-dose Healthy Subject Studies by Pooled Dose Group

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=49) n (%)	>200 - <=400 mcg (N=21) n (%)	>400 mcg (N=12) n (%)	Overall (N=82) n (%)
At least one serious TEAE	1 (2.0)	0	0	1 (1.2)
Gastrointestinal disorders	1 (2.0)	0	0	1 (1.2)
Vomiting	1 (2.0)	0	0	1 (1.2)

Source: Integrated Summary of Safety, Table 12.3.1, P. 3016 of 4367.

Table 26: Serious Adverse Events Reported in the Single-dose Cancer Studies

	Dose			
System Organ Class Preferred Term	100 mcg (N=38) n (%)	200 mcg (N=37) n (%)	400 mcg (N=34) n (%)	Placebo (N=27) n (%)
At least one serious TEAE	1 (2.6)	0	1 (2.9)	0
General disorders and administration site conditions	1 (2.6)	0	0	0
General physical health deterioration	1 (2.6)	0	0	0
Pain	1 (2.6)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (2.9)	0
Malignant neoplasm progression	0	0	1 (2.9)	0

Source: Integrated Summary of Safety, Table 12.4, P. 3017 of 4367.

Table 27: Serious Adverse Events Reported in the Single-dose Cancer Studies by Pooled Dose Group

System Organ Class Preferred Term	Pooled Dose Group <=200 mcg (N=39) n (%)	 >200 - <=400 mcg (N=34) n (%)	 >400 mcg (N=0) n (%)	 Overall (N=41) n (%)
At least one serious TEAE	1 (2.6)	1 (2.9)	0	2 (4.9)
General disorders and administration site conditions	1 (2.6)	0	0	1 (2.4)
General physical health deterioration	1 (2.6)	0	0	1 (2.4)
Pain	1 (2.6)	0	0	1 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.9)	0	1 (2.4)
Malignant neoplasm progression	0	1 (2.9)	0	1 (2.4)

Source: Integrated Summary of Safety, Table 12.4.1, P. 3018 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies

System Organ Class Preferred Term	Dose 100 mcg (N=22) n (%)	 200 mcg (N=26) n (%)	 300 mcg (N=58) n (%)	 400 mcg (N=45) n (%)	 600 mcg (N=66) n (%)	 800 mcg (N=105) n (%)
At least one serious TEAE	2 (9.1)	8 (30.8)	13 (22.4)	6 (13.3)	15 (22.7)	26 (24.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (15.4)	4 (6.9)	1 (2.2)	7 (10.6)	14 (13.3)
Prostate cancer metastatic	0	1 (3.8)	2 (3.4)	0	1 (1.5)	3 (2.9)
Breast cancer metastatic	0	2 (7.7)	1 (1.7)	0	0	1 (1.0)
Lung cancer metastatic	0	0	0	0	1 (1.5)	2 (1.9)
Cancer pain	0	0	0	0	2 (3.0)	0
Colon cancer metastatic	0	1 (3.8)	0	0	0	1 (1.0)
Metastatic carcinoma of the bladder	0	0	0	0	0	2 (1.9)
Metastatic renal cell carcinoma	0	0	0	0	1 (1.5)	1 (1.0)
Non-small cell lung cancer metastatic	0	0	0	0	1 (1.5)	1 (1.0)
Oesophageal cancer metastatic	0	0	1 (1.7)	0	1 (1.5)	0
Metastatic gastric cancer	0	0	0	0	0	1 (1.0)
Metastatic pain	0	0	0	0	0	1 (1.0)
Pancreatic carcinoma metastatic	0	0	0	0	0	1 (1.0)
Renal cancer metastatic	0	0	0	1 (2.2)	0	0
Retro-orbital neoplasm	0	0	0	0	0	1 (1.0)
Infections and infestations	1 (4.5)	2 (7.7)	1 (1.7)	1 (2.2)	4 (6.1)	8 (7.6)
Pneumonia	0	0	1 (1.7)	0	1 (1.5)	4 (3.8)
Central line infection	0	1 (3.8)	0	0	0	1 (1.0)
Bronchitis	0	0	0	0	0	1 (1.0)

Source: Integrated Summary of Safety, Table 12.5, P. 3019 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

System Organ Class Preferred Term	Dose 100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Infections and infestations (cont'd)						
Candida sepsis	0	0	0	1 (2.2)	0	0
Cellulitis	0	1 (3.8)	0	0	0	0
Intestinal fistula infection	0	0	0	0	1 (1.5)	0
Lobar pneumonia	0	0	0	0	0	1 (1.0)
Lung infection	0	0	1 (1.7)	0	0	0
Pneumonia herpes viral	0	0	0	0	1 (1.5)	0
Sepsis	0	0	0	0	0	1 (1.0)
Septic shock	1 (4.5)	0	0	0	0	0
Wound infection staphylococcal	0	0	0	0	1 (1.5)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.7)	2 (4.4)	4 (6.1)	4 (3.8)
Pulmonary embolism	0	0	0	0	1 (1.5)	2 (1.9)
Respiratory failure	0	0	0	0	1 (1.5)	1 (1.0)
Alveolitis allergic	0	0	0	0	0	1 (1.0)
Chronic obstructive pulmonary disease	0	0	0	1 (2.2)	0	0
Hypoxia	0	0	0	1 (2.2)	0	0
Pleural effusion	0	0	0	0	1 (1.5)	0
Pneumothorax	0	0	0	0	1 (1.5)	0
Pulmonary oedema	0	0	0	0	0	1 (1.0)
Pulmonary thrombosis	0	0	1 (1.7)	0	0	0

Source: Integrated Summary of Safety, Table 12.5, P. 3020 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

System Organ Class Preferred Term	Dose 100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Blood and lymphatic system disorders	0	3 (11.5)	0	1 (2.2)	3 (4.5)	2 (1.9)
Anaemia	0	1 (3.8)	0	0	1 (1.5)	2 (1.9)
Febrile neutropenia	0	1 (3.8)	0	1 (2.2)	1 (1.5)	0
Pancytopenia	0	0	0	0	2 (3.0)	0
Coagulopathy	0	1 (3.8)	0	0	0	0
Gastrointestinal disorders	1 (4.5)	0	2 (3.4)	1 (2.2)	3 (4.5)	1 (1.0)
Dysphagia	0	0	1 (1.7)	0	1 (1.5)	0
Abdominal pain	0	0	0	0	1 (1.5)	0
Gastrointestinal disorder	0	0	0	0	1 (1.5)	0
Gastrointestinal haemorrhage	1 (4.5)	0	0	0	0	0
Intestinal obstruction	0	0	0	0	0	1 (1.0)
Nausea	0	0	0	1 (2.2)	0	0
Small intestinal obstruction	0	0	1 (1.7)	0	0	0
Vomiting	0	0	0	1 (2.2)	0	0
Cardiac disorders	0	1 (3.8)	2 (3.4)	0	2 (3.0)	2 (1.9)
Acute coronary syndrome	0	0	1 (1.7)	0	0	0
Cardiac failure congestive	0	0	0	0	0	1 (1.0)
Cardio-respiratory arrest	0	1 (3.8)	0	0	0	0
Myocardial infarction	0	0	1 (1.7)	0	0	0
Myocardial ischaemia	0	0	0	0	1 (1.5)	0
Supraventricular tachycardia	0	0	0	0	0	1 (1.0)

Source: Integrated Summary of Safety, Table 12.5, P. 3021 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

	Dose					
System Organ Class Preferred Term	100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Cardiac disorders (cont'd)						
Ventricular tachycardia	0	0	0	0	1 (1.5)	0
Metabolism and nutrition disorders	0	1 (3.8)	1 (1.7)	2 (4.4)	2 (3.0)	1 (1.0)
Dehydration	0	1 (3.8)	1 (1.7)	2 (4.4)	2 (3.0)	0
Hyponatraemia	0	0	0	0	1 (1.5)	1 (1.0)
General disorders and administration site conditions	0	2 (7.7)	1 (1.7)	0	1 (1.5)	2 (1.9)
Pain	0	0	1 (1.7)	0	0	2 (1.9)
Asthenia	0	0	0	0	1 (1.5)	0
Chest pain	0	1 (3.8)	0	0	0	0
Infusion site reaction	0	1 (3.8)	0	0	0	0
Nervous system disorders	0	0	0	0	1 (1.5)	4 (3.8)
Convulsion	0	0	0	0	0	2 (1.9)
Dizziness	0	0	0	0	0	1 (1.0)
Dyskinesia	0	0	0	0	1 (1.5)	0
Spinal cord compression	0	0	0	0	0	1 (1.0)
Vascular disorders	0	0	0	1 (2.2)	2 (3.0)	2 (1.9)
Deep vein thrombosis	0	0	0	0	1 (1.5)	1 (1.0)
Hypotension	0	0	0	0	1 (1.5)	0

Source: Integrated Summary of Safety, Table 12.5, P. 3022 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

	Dose					
System Organ Class Preferred Term	100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Vascular disorders (cont'd)						
Orthostatic hypotension	0	0	0	1 (2.2)	0	0
Subclavian vein thrombosis	0	0	0	0	0	1 (1.0)
Psychiatric disorders	1 (4.5)	0	1 (1.7)	0	0	2 (1.9)
Acute psychosis	0	0	0	0	0	1 (1.0)
Affect lability	1 (4.5)	0	0	0	0	0
Completed suicide	0	0	0	0	0	1 (1.0)
Confusional state	0	0	1 (1.7)	0	0	0
Suicide attempt	0	0	0	0	0	1 (1.0)
Hepatobiliary disorders	0	0	0	1 (2.2)	1 (1.5)	1 (1.0)
Cholecystitis	0	0	0	1 (2.2)	1 (1.5)	0
Cholecystitis acute	0	0	0	0	0	1 (1.0)
Renal and urinary disorders	0	0	2 (3.4)	1 (2.2)	0	0
Azotaemia	0	0	1 (1.7)	0	0	0
Haematuria	0	0	0	1 (2.2)	0	0
Obstructive uropathy	0	0	0	1 (2.2)	0	0
Renal failure acute	0	0	1 (1.7)	0	0	0
Urinary retention	0	0	1 (1.7)	0	0	0

Source: Integrated Summary of Safety, Table 12.5, P. 3023 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

	Dose					
System Organ Class Preferred Term	100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Injury, poisoning and procedural complications	0	0	0	0	1 (1.5)	1 (1.0)
Radiation pneumonitis	0	0	0	0	1 (1.5)	0
Spinal compression fracture	0	0	0	0	0	1 (1.0)
Musculoskeletal and connective tissue disorders	0	1 (3.8)	0	0	0	1 (1.0)
Arthritis	0	0	0	0	0	1 (1.0)
Back pain	0	1 (3.8)	0	0	0	0
Immune system disorders	0	0	1 (1.7)	0	0	0
Immunosuppression	0	0	1 (1.7)	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (1.5)	0
Leukocytoclastic vasculitis	0	0	0	0	1 (1.5)	0

Source: Integrated Summary of Safety, Table 12.5, P. 3024 of 4367.

Table 28: Serious Adverse Events Reported in the Multiple-dose Cancer Studies (cont.)

	Dose					
System Organ Class Preferred Term	100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
Blood and lymphatic system disorders	0	3 (11.5)	0	1 (2.2)	3 (4.5)	2 (1.9)
Anaemia	0	1 (3.8)	0	0	1 (1.5)	2 (1.9)
Febrile neutropenia	0	1 (3.8)	0	1 (2.2)	1 (1.5)	0
Pancytopenia	0	0	0	0	2 (3.0)	0
Coagulopathy	0	1 (3.8)	0	0	0	0
Gastrointestinal disorders	1 (4.5)	0	2 (3.4)	1 (2.2)	3 (4.5)	1 (1.0)
Dysphagia	0	0	1 (1.7)	0	1 (1.5)	0
Abdominal pain	0	0	0	0	1 (1.5)	0
Gastrointestinal disorder	0	0	0	0	1 (1.5)	0
Gastrointestinal haemorrhage	1 (4.5)	0	0	0	0	0
Intestinal obstruction	0	0	0	0	0	1 (1.0)
Nausea	0	0	0	1 (2.2)	0	0
Small intestinal obstruction	0	0	1 (1.7)	0	0	0
Vomiting	0	0	0	1 (2.2)	0	0
Cardiac disorders	0	1 (3.8)	2 (3.4)	0	2 (3.0)	2 (1.9)
Acute coronary syndrome	0	0	1 (1.7)	0	0	0
Cardiac failure congestive	0	0	0	0	0	1 (1.0)
Cardio-respiratory arrest	0	1 (3.8)	0	0	0	0
Myocardial infarction	0	0	1 (1.7)	0	0	0
Myocardial ischaemia	0	0	0	0	1 (1.5)	0
Supraventricular tachycardia	0	0	0	0	0	1 (1.0)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3025 of 4367.

Table 29: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Pooled Dose Group

System Organ Class Preferred Term	Pooled Dose Group <=200 mcg (N=45) n (%)	 >200 - <=400 mcg (N=98) n (%)	 >400 mcg (N=152) n (%)	 Overall (N=270) n (%)
Infections and infestations (cont'd)				
Candida sepsis	0	1 (1.0)	0	1 (0.4)
Cellulitis	1 (2.2)	0	0	1 (0.4)
Intestinal fistula infection	0	0	1 (0.7)	1 (0.4)
Lobar pneumonia	0	0	1 (0.7)	1 (0.4)
Lung infection	0	1 (1.0)	0	1 (0.4)
Pneumonia herpes viral	0	0	1 (0.7)	1 (0.4)
Sepsis	0	0	1 (0.7)	1 (0.4)
Septic shock	1 (2.2)	0	0	1 (0.4)
Wound infection staphylococcal	0	0	1 (0.7)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	3 (3.1)	8 (5.3)	11 (4.1)
Pulmonary embolism	0	0	3 (2.0)	3 (1.1)
Respiratory failure	0	0	2 (1.3)	2 (0.7)
Alveolitis allergic	0	0	1 (0.7)	1 (0.4)
Chronic obstructive pulmonary disease	0	1 (1.0)	0	1 (0.4)
Hypoxia	0	1 (1.0)	0	1 (0.4)
Pleural effusion	0	0	1 (0.7)	1 (0.4)
Pneumothorax	0	0	1 (0.7)	1 (0.4)
Pulmonary oedema	0	0	1 (0.7)	1 (0.4)
Pulmonary thrombosis	0	1 (1.0)	0	1 (0.4)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3026 of 4367.

Table 29: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Pooled Dose Group (cont.)

System Organ Class Preferred Term	Pooled Dose Group <=200 mcg (N=45) n (%)	 >200 - <=400 mcg (N=98) n (%)	 >400 mcg (N=152) n (%)	 Overall (N=270) n (%)
Blood and lymphatic system disorders	3 (6.7)	1 (1.0)	5 (3.3)	9 (3.3)
Anaemia	1 (2.2)	0	3 (2.0)	4 (1.5)
Febrile neutropenia	1 (2.2)	1 (1.0)	1 (0.7)	3 (1.1)
Pancytopenia	0	0	2 (1.3)	2 (0.7)
Coagulopathy	1 (2.2)	0	0	1 (0.4)
Gastrointestinal disorders	1 (2.2)	3 (3.1)	4 (2.6)	8 (3.0)
Dysphagia	0	1 (1.0)	1 (0.7)	2 (0.7)
Abdominal pain	0	0	1 (0.7)	1 (0.4)
Gastrointestinal disorder	0	0	1 (0.7)	1 (0.4)
Gastrointestinal haemorrhage	1 (2.2)	0	0	1 (0.4)
Intestinal obstruction	0	0	1 (0.7)	1 (0.4)
Nausea	0	1 (1.0)	0	1 (0.4)
Small intestinal obstruction	0	1 (1.0)	0	1 (0.4)
Vomiting	0	1 (1.0)	0	1 (0.4)
Cardiac disorders	1 (2.2)	2 (2.0)	4 (2.6)	7 (2.6)
Acute coronary syndrome	0	1 (1.0)	0	1 (0.4)
Cardiac failure congestive	0	0	1 (0.7)	1 (0.4)
Cardio-respiratory arrest	1 (2.2)	0	0	1 (0.4)
Myocardial infarction	0	1 (1.0)	0	1 (0.4)
Myocardial ischaemia	0	0	1 (0.7)	1 (0.4)
Supraventricular tachycardia	0	0	1 (0.7)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3027 of 4367.

Table 29: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Pooled Dose Group (cont.)

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=45) n (%)	>200 - <=400 mcg (N=98) n (%)	>400 mcg (N=152) n (%)	Overall (N=270) n (%)
Cardiac disorders (cont'd)				
Ventricular tachycardia	0	0	1 (0.7)	1 (0.4)
Metabolism and nutrition disorders	1 (2.2)	3 (3.1)	3 (2.0)	7 (2.6)
Dehydration	1 (2.2)	3 (3.1)	2 (1.3)	6 (2.2)
Hyponatraemia	0	0	2 (1.3)	2 (0.7)
General disorders and administration site conditions	2 (4.4)	1 (1.0)	3 (2.0)	6 (2.2)
Pain	0	1 (1.0)	2 (1.3)	3 (1.1)
Asthenia	0	0	1 (0.7)	1 (0.4)
Chest pain	1 (2.2)	0	0	1 (0.4)
Infusion site reaction	1 (2.2)	0	0	1 (0.4)
Nervous system disorders	0	0	5 (3.3)	5 (1.9)
Convulsion	0	0	2 (1.3)	2 (0.7)
Dizziness	0	0	1 (0.7)	1 (0.4)
Dyskinesia	0	0	1 (0.7)	1 (0.4)
Spinal cord compression	0	0	1 (0.7)	1 (0.4)
Vascular disorders	0	1 (1.0)	4 (2.6)	5 (1.9)
Deep vein thrombosis	0	0	2 (1.3)	2 (0.7)
Hypotension	0	0	1 (0.7)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3028 of 4367.

Table 29: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Pooled Dose Group (cont.)

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=45) n (%)	>200 - <=400 mcg (N=98) n (%)	>400 mcg (N=152) n (%)	Overall (N=270) n (%)
Vascular disorders (cont'd)				
Orthostatic hypotension	0	1 (1.0)	0	1 (0.4)
Subclavian vein thrombosis	0	0	1 (0.7)	1 (0.4)
Psychiatric disorders	1 (2.2)	1 (1.0)	2 (1.3)	4 (1.5)
Acute psychosis	0	0	1 (0.7)	1 (0.4)
Affect lability	1 (2.2)	0	0	1 (0.4)
Completed suicide	0	0	1 (0.7)	1 (0.4)
Confusional state	0	1 (1.0)	0	1 (0.4)
Suicide attempt	0	0	1 (0.7)	1 (0.4)
Hepatobiliary disorders	0	1 (1.0)	2 (1.3)	3 (1.1)
Cholecystitis	0	1 (1.0)	1 (0.7)	2 (0.7)
Cholecystitis acute	0	0	1 (0.7)	1 (0.4)
Renal and urinary disorders	0	3 (3.1)	0	3 (1.1)
Azotaemia	0	1 (1.0)	0	1 (0.4)
Haematuria	0	1 (1.0)	0	1 (0.4)
Obstructive uropathy	0	1 (1.0)	0	1 (0.4)
Renal failure acute	0	1 (1.0)	0	1 (0.4)
Urinary retention	0	1 (1.0)	0	1 (0.4)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3029 of 4367.

Table 29: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Pooled Dose Group (cont.)

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=45) n (%)	>200 - <=400 mcg (N=98) n (%)	>400 mcg (N=152) n (%)	Overall (N=270) n (%)
Injury, poisoning and procedural complications	0	0	2 (1.3)	2 (0.7)
Radiation pneumonitis	0	0	1 (0.7)	1 (0.4)
Spinal compression fracture	0	0	1 (0.7)	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (2.2)	0	1 (0.7)	2 (0.7)
Arthritis	0	0	1 (0.7)	1 (0.4)
Back pain	1 (2.2)	0	0	1 (0.4)
Immune system disorders	0	1 (1.0)	0	1 (0.4)
Immunosuppression	0	1 (1.0)	0	1 (0.4)
Skin and subcutaneous tissue disorders	0	0	1 (0.7)	1 (0.4)
Leukocytoclastic vasculitis	0	0	1 (0.7)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.5.1, P. 3030 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase

	Completed Open-label Titration Phase (N=270) n(%)		Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
System Organ Class Preferred Term	No (N=96)	Yes (N=174)			
At least one serious TEAE	12 (12.5)	1 (0.6)	0	58 (34.5)	70 (25.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (6.3)	0	0	24 (14.3)	30 (11.1)
Prostate cancer metastatic	2 (2.1)	0	0	5 (3.0)	7 (2.6)
Breast cancer metastatic	1 (1.0)	0	0	3 (1.8)	4 (1.5)
Lung cancer metastatic	0	0	0	3 (1.8)	3 (1.1)
Cancer pain	0	0	0	2 (1.2)	2 (0.7)
Colon cancer metastatic	0	0	0	2 (1.2)	2 (0.7)
Metastatic carcinoma of the bladder	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Metastatic renal cell carcinoma	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Non-small cell lung cancer metastatic	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Oesophageal cancer metastatic	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Metastatic gastric cancer	0	0	0	1 (0.6)	1 (0.4)
Metastatic pain	0	0	0	1 (0.6)	1 (0.4)
Pancreatic carcinoma metastatic	0	0	0	1 (0.6)	1 (0.4)
Renal cancer metastatic	0	0	0	1 (0.6)	1 (0.4)
Retro-orbital neoplasm	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3031 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
Infections and infestations	0	0	0	17 (10.1)	17 (6.3)
Pneumonia	0	0	0	6 (3.6)	6 (2.2)
Central line infection	0	0	0	2 (1.2)	2 (0.7)
Bronchitis	0	0	0	1 (0.6)	1 (0.4)
Candida sepsis	0	0	0	1 (0.6)	1 (0.4)
Cellulitis	0	0	0	1 (0.6)	1 (0.4)
Intestinal fistula infection	0	0	0	1 (0.6)	1 (0.4)
Lobar pneumonia	0	0	0	1 (0.6)	1 (0.4)
Lung infection	0	0	0	1 (0.6)	1 (0.4)
Pneumonia herpes viral	0	0	0	1 (0.6)	1 (0.4)
Sepsis	0	0	0	1 (0.6)	1 (0.4)
Septic shock	0	0	0	1 (0.6)	1 (0.4)
Wound infection staphylococcal	0	0	0	1 (0.6)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	0	0	11 (6.5)	11 (4.1)
Pulmonary embolism	0	0	0	3 (1.8)	3 (1.1)
Respiratory failure	0	0	0	2 (1.2)	2 (0.7)
Alveolitis allergic	0	0	0	1 (0.6)	1 (0.4)
Chronic obstructive pulmonary disease	0	0	0	1 (0.6)	1 (0.4)
Hypoxia	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3032 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
Respiratory, thoracic and mediastinal disorders (cont'd)					
Pleural effusion	0	0	0	1 (0.6)	1 (0.4)
Pneumothorax	0	0	0	1 (0.6)	1 (0.4)
Pulmonary oedema	0	0	0	1 (0.6)	1 (0.4)
Pulmonary thrombosis	0	0	0	1 (0.6)	1 (0.4)
Blood and lymphatic system disorders	0	1 (0.6)	0	9 (5.4)	9 (3.3)
Anaemia	0	0	0	4 (2.4)	4 (1.5)
Febrile neutropenia	0	1 (0.6)	0	3 (1.8)	3 (1.1)
Pancytopenia	0	0	0	2 (1.2)	2 (0.7)
Coagulopathy	0	0	0	1 (0.6)	1 (0.4)
Gastrointestinal disorders	1 (1.0)	0	0	7 (4.2)	8 (3.0)
Dysphagia	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Abdominal pain	0	0	0	1 (0.6)	1 (0.4)
Gastrointestinal disorder	0	0	0	1 (0.6)	1 (0.4)
Gastrointestinal haemorrhage	0	0	0	1 (0.6)	1 (0.4)
Intestinal obstruction	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3033 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
Gastrointestinal disorders (cont'd)					
Nausea	0	0	0	1 (0.6)	1 (0.4)
Small intestinal obstruction	0	0	0	1 (0.6)	1 (0.4)
Vomiting	0	0	0	1 (0.6)	1 (0.4)
Cardiac disorders	2 (2.1)	0	0	5 (3.0)	7 (2.6)
Acute coronary syndrome	0	0	0	1 (0.6)	1 (0.4)
Cardiac failure congestive	0	0	0	1 (0.6)	1 (0.4)
Cardio-respiratory arrest	1 (1.0)	0	0	0	1 (0.4)
Myocardial infarction	0	0	0	1 (0.6)	1 (0.4)
Myocardial ischaemia	0	0	0	1 (0.6)	1 (0.4)
Supraventricular tachycardia	1 (1.0)	0	0	0	1 (0.4)
Ventricular tachycardia	0	0	0	1 (0.6)	1 (0.4)
Metabolism and nutrition disorders	0	0	0	7 (4.2)	7 (2.6)
Dehydration	0	0	0	6 (3.6)	6 (2.2)
Hyponatraemia	0	0	0	2 (1.2)	2 (0.7)

Source: Integrated Summary of Safety, Table 12.6, P. 3034 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
General disorders and administration site conditions	2 (2.1)	0	0	4 (2.4)	6 (2.2)
Pain	1 (1.0)	0	0	2 (1.2)	3 (1.1)
Asthenia	0	0	0	1 (0.6)	1 (0.4)
Chest pain	1 (1.0)	0	0	0	1 (0.4)
Infusion site reaction	0	0	0	1 (0.6)	1 (0.4)
Nervous system disorders	0	0	0	5 (3.0)	5 (1.9)
Convulsion	0	0	0	2 (1.2)	2 (0.7)
Dizziness	0	0	0	1 (0.6)	1 (0.4)
Dyskinesia	0	0	0	1 (0.6)	1 (0.4)
Spinal cord compression	0	0	0	1 (0.6)	1 (0.4)
Vascular disorders	0	0	0	5 (3.0)	5 (1.9)
Deep vein thrombosis	0	0	0	2 (1.2)	2 (0.7)
Hypotension	0	0	0	1 (0.6)	1 (0.4)
Orthostatic hypotension	0	0	0	1 (0.6)	1 (0.4)
Subclavian vein thrombosis	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3035 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
Psychiatric disorders	2 (2.1)	0	0	2 (1.2)	4 (1.5)
Acute psychosis	0	0	0	1 (0.6)	1 (0.4)
Affect lability	1 (1.0)	0	0	0	1 (0.4)
Completed suicide	0	0	0	1 (0.6)	1 (0.4)
Confusional state	1 (1.0)	0	0	0	1 (0.4)
Suicide attempt	0	0	0	1 (0.6)	1 (0.4)
Hepatobiliary disorders	0	0	0	3 (1.8)	3 (1.1)
Cholecystitis	0	0	0	2 (1.2)	2 (0.7)
Cholecystitis acute	0	0	0	1 (0.6)	1 (0.4)
Renal and urinary disorders	2 (2.1)	0	0	1 (0.6)	3 (1.1)
Azotaemia	1 (1.0)	0	0	0	1 (0.4)
Haematuria	1 (1.0)	0	0	0	1 (0.4)
Obstructive uropathy	1 (1.0)	0	0	0	1 (0.4)
Renal failure acute	1 (1.0)	0	0	0	1 (0.4)
Urinary retention	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3036 of 4367.

Table 30: Serious Adverse Events Reported in the Multiple-dose Cancer Studies by Study Phase (cont.)

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%) No (N=96)	 Yes (N=174)	Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
Injury, poisoning and procedural complications	0	0	0	2 (1.2)	2 (0.7)
Radiation pneumonitis	0	0	0	1 (0.6)	1 (0.4)
Spinal compression fracture	0	0	0	1 (0.6)	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	0	2 (1.2)	2 (0.7)
Arthritis	0	0	0	1 (0.6)	1 (0.4)
Back pain	0	0	0	1 (0.6)	1 (0.4)
Immune system disorders	0	0	0	1 (0.6)	1 (0.4)
Immunosuppression	0	0	0	1 (0.6)	1 (0.4)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.6)	1 (0.4)
Leukocytoclastic vasculitis	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 12.6, P. 3037 of 4367.

9.5 Narratives of Subjects Who Withdrew Consent

EN3267-005 Withdrawal - Open-Label Titration Phase

Patient No.: 509502
Case No(s).: Not applicable
Event(s): Withdrawn consent – diary too confusing
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 61-year-old male took EN3267 as needed starting on 04 May 2006 for episodes of breakthrough cancer pain and was taking 600 µg sublingual tablets during the open-label titration phase of the study. Relevant medical history included depression and alcoholism. Other medical history included anemia of chronic disease, node dissection, syncope, autonomic hypotension, hypothyroidism, abdominal pain, constipation, gastric reflux, peristalsis, esophageal stricture, gout, muscular dystrophy due to radiation, autonomic dysfunction (seizure), cachexia, chronic obstructive pulmonary disease, aspiration pneumonia and pale skin. Relevant concomitant medications included amitriptyline, clonazepam and escitalopram. The patient was also taking allopurinol, epoetin alfa, esomeprazole, fentanyl transdermal, folic acid, lactulose, levothyroxine, loperamide, metoclopramide, morphine, nutritional supplement and phenytoin. The patient took his last study drug dose on 15 May 2006 and discontinued from the study on 16 May 2006. He discontinued from the study because he found the diary too confusing to complete.

Patient No.: 519503
Case No(s).: Not applicable
Event(s): Withdrawn consent – felt it was not the right time to do the study
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 62-year-old female took EN3267 as needed starting on 13 Jun 2006 for episodes of breakthrough cancer pain and was taking 100 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included bilateral edema, anorexia due to decreased appetite which resulted in weight loss, diarrhea, pain in abdominal area, pancreatic cancer, diabetes mellitus, anemia, carpal tunnel right wrist problem, chronic low back pain due to auto accident, allergic to codeine and morphine, fatigue, carpal tunnel surgery, cesarean section surgery and Port-a-Cath placement. The patient's concomitant medications included calcium gluconate, dexamethasone, diphenoxylate and atropine sulfate, erythropoietin, gemcitabine, glipizide, granisetron hydrochloride, hydrocodone and acetaminophen, iron preparations, magnesium sulfate, oxaliplatin, oxycodone hydrochloride, rosiglitazone maleate and spironolactone. This patient took her last study drug dose on 15 Jun 2006 and discontinued from the study on 19 Jun 2006. She discontinued from the study because she felt that it was not the right time to do the study.

Patient No.: 535502
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 48-year-old female took EN3267 as needed starting on 11 May 2007 for episodes of breakthrough cancer pain and was taking 800 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included adenoidectomy, tonsillectomy, indigestion, neuropathic pain left chest, neuropathic pain left axillary, bone marrow transplant, breast cancer, left lymph node dissection, right lymph node biopsy, dorsal flap reconstruction (left breast), depression and allergies to latex, morphine and penicillin. The patient's concomitant medications included alendronate, bupropion, letrozole, methadone, oxycodone and pregabalin. This patient took her last study drug dose on 29 May 2007 and discontinued from the study on 04 Jun 2007. She discontinued from the study because she withdrew consent. The reason for withdrawal of consent was not stated.

Patient No.: 539513
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 71-year-old male took EN3267 as needed starting on 19 Mar 2008 for episodes of breakthrough cancer pain and was taking 800 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included keloid scar behind right ear, night sweats, scar right hip, transverse scar right lower quadrant, sleep apnea, hypertension, appendectomy, constipation, gallstone, nausea, ruptured appendix, fever, prostate cancer, prostate enlargement, cervical spondylosis, difficulty walking, diffuse musculoskeletal pain, generalized tenderness (ribs and back), gouty arthropathy, left foot to ankle pain, left hip fracture and repair, lumbar degenerative disc disease, osteoarthritis, right leg pain, secondary malignant neoplasm of bone and bone marrow, allergy to intravenous pyelogram dye, anxiety, depression and insomnia. The patient's concomitant medications included allopurinol, alprazolam, amitriptyline, amlodipine, bupropion, eszopiclone, fentanyl, leuprolide, lubiprostone, multivitamins, oxycodone and acetaminophen, polyethylene glycol and tamsulosin. This patient took his last study drug dose on 27 Mar 2008 and discontinued from the study on 28 Mar 2008. He discontinued from the study because of withdrawn consent. The reason for withdrawal of consent was not stated.

Patient No.: 548504
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 56-year-old female took EN3267 as needed starting on 07 Jul 2006 for episodes of breakthrough cancer pain and was taking 400 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included constipation, dilatation of ureteral stricture, hysterectomy, incontinence of urine, tubal ligation, anemia, multiple myeloma and cancer-related back pain. The patient's concomitant medications included acyclovir, clotrimazole, dexamethasone, ketoconazole, morphine, oxycodone, pentosan polysulfate, sodium phosphate and thalidomide. The patient took her last dose of study drug on 17 Jul 2006 and discontinued from the study on 20 Jul 2006. She discontinued from the study because she withdrew consent. The reason for withdrawal of consent was not stated.

Patient No.: 559501
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 46-year-old male took EN3267 as needed starting on 06 Feb 2007 for episodes of breakthrough cancer pain and was taking 400 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included migraine, missing teeth, right ear hearing loss, smoking, abdominal pain, colon cancer, left colostomy, hernia, impotence, infection anal area, ingrowing tissues, nocturia, bilateral upper extremities weakness, cervical neck pain, leg pain, lower back pain, right leg weakness, hepatitis B and C and depression. The patient's concomitant medications included alprazolam, hydrocodone and hydromorphone. This patient took his last study drug dose on 04 Mar 2007 and discontinued from the study on 03 Apr 2007. He discontinued from the study because he withdrew consent. The reason for withdrawal of consent was not stated.

Patient No.: 561506
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 56-year-old female took EN3267 as needed starting on 07 Jan 2007 for episodes of breakthrough cancer pain and was taking 600 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included alopecia, cushingoid facies, thrush, lung metastases, persistent cough, pleural effusion, atrial enlargement, blood clots in legs, old interior infarct, constipation, brain metastases, cancer-related pain in thigh, pain related to blood clots, pedal edema, breast cancer,

double mastectomy, spinal cord compression, tender right calf and tender sacral area due to a deformed coccyx. The patient's concomitant medications included benzonatate, darbepoetin, dexamethasone, dextrose and sodium chloride, diphenhydramine, famotidine, filgrastim, ioversol, lactulose, methylprednisolone, metoclopramide, morphine, oxycodone and acetaminophen, prochlorperazine, senna and warfarin. This patient took her last study drug dose on 07 Jan 2008 and discontinued from the study on 11 Jan 2008. She discontinued from the study because she withdrew consent. The reason for withdrawal of consent was not stated.

Patient No.: 561509
Case No(s).: Not applicable
Event(s): Withdrawn consent – study drug made him feel sick
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 60-year-old male took EN3267 as needed starting on 18 Jul 2008 for episodes of breakthrough cancer pain and was taking 100 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included headaches, bilateral lung masses, chronic obstructive pulmonary disease, mediastinal adenopathy, metastatic non-small cell lung cancer, positive tuberculin skin test (nonactive), smoking, shortness of breath, 3 stents in heart, coronary artery disease, port placement, venofibrosis, anorexia, constipation, diarrhea, gastroesophageal reflux disease, intermittent dysphagia and mucositis, confusion, intermittent epistaxis and neutropenia, mouth ulcers, odynophagia, hypercholesterolemia, bilateral neuropathy in hands, anemia, hyperlipidemia, thrombocytopenia, cancer-related low back pain, knee surgeries (both knees), allergy to heart catheter iodine, depression related to disease and esophageal ulcer. The patient's concomitant medications included acetylsalicylic acid, cyanocobalamin, dexamethasone, erythropoietin, esomeprazole, filgrastim, folic acid, ibuprofen, ipratropium, megestrol, morphine, oxycodone and acetaminophen, oprelvekin, prochlorperazine, promethazine, pyridoxine, salbutamol and Senna alexandrina. This patient only took study drug on 18 Jul 2008 and discontinued from the study on 25 Jul 2008. He discontinued from the study because the study drug made him feel sick.

Patient No.: 563501
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 39-year-old female took EN3267 as needed starting on 19 Mar 2007 for episodes of breakthrough cancer pain and was taking 400 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included chronic cancer-related bilateral abdominal pain in lower quadrant, bilateral tubal ligation, cervical cancer, laser surgery for cervical cancer, uterine fibroids, chronic low back pain, soreness left thigh and allergies to acetaminophen/propoxyphene and naproxen. The

patient's concomitant medications included carisoprodol and hydrocodone and acetaminophen. This patient took her last study drug dose on 30 Mar 2007 and discontinued from the study on 02 Apr 2007. She discontinued from the study because she withdrew consent. The reason for withdrawal of consent was not stated.

Patient No.: 565501
Case No(s).: Not applicable
Event(s): Withdrawn consent – pain increase
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 79-year-old male took EN3267 as needed starting on 25 Apr 2007 for episodes of breakthrough cancer pain and was taking 200 µg sublingual tablets during the open-label titration phase of the study. The patient's medical history included shingles, poor dentition, chronic obstructive pulmonary disease, malignant lung mass, non-small cell lung cancer, possible lung abscess, deep vein thrombosis secondary to Mediport (implantable vascular access port), hypertension, no pedal pulses, peripheral artery disease, appendicitis, duodenal ulcer, gastric ulcer, gastritis, internal hemorrhoids, melena, nausea, opiate-induced constipation, left renal mass, anemia, back pain, chronic left shoulder pain, degenerative joint disease, cancer pain and weight loss secondary to cancer. The patient's concomitant medications included atenolol, clindamycin, docusate, fentanyl, folic acid, hydrochlorothiazide, iron, omeprazole, oxycodone and acetaminophen and prochlorperazine. The patient took his last study drug dose on 28 Apr 2007 and discontinued from the study on 30 Apr 2007. He discontinued from the study because he had a quick increase in pain and little long-term efficacy in pain relief and withdrew his consent.

EN3267-005 Withdrawals - Double-Blind Study Phase

Patient No.: 518502
Case No(s).: Not applicable
Event(s): Withdrawn consent – medication did not last as long as previous medication
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 56-year-old male took EN3267 as needed starting on 05 Jul 2006 for episodes of breakthrough cancer pain and was taking 100 to 400 µg sublingual tablets during the double-blind treatment phase of the study. The patient's medical history included well-healed surgical scars, dental caries, periodontal disease, abdominal aortic aneurysm, hypertension, right bundle branch block, colon cancer, right upper quadrant/right flank pain, hyperlipidemia, hypogonadism, anemia, multiple surgeries for trauma to extremities, status post partial hepatectomy for colon cancer metastasis and posttraumatic stress disorder with depression. The patient's concomitant medications included furosemide, gemfibrozil, hydrochlorothiazide, oxycodone and acetaminophen and ramipril. The patient took his last study drug dose on 21 Jul 2006 and discontinued from the study on 28 Jul 2006. He discontinued from the study because the medication did not last as long as his prior breakthrough pain medication.

Patient No.: 523501
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 61-year-old male took EN3267 as needed starting on 10 Aug 2006 for episodes of breakthrough cancer pain and was taking 100 to 400 µg sublingual tablets during the double-blind treatment phase of the study. The patient's medical history included pallor, dysphagia, chronic obstructive pulmonary disease, emphysema, lung cancer, pericardial effusion, pneumonitis, cardiac murmur, carotid calcifications, intermittent lower extremity edema, upper extremity edema, constipation, gastroesophageal reflux disease, intermittent nausea, vomiting, neuropathic pain, renal cysts, urinary difficulty, back pain, hyporeflexia, intermittent chest pain, shoulder pain, anemia, elevated platelets, elevated white blood cell, hyperkalemia, cervical spondylosis, compression fracture T12 and L1, degenerative joint disease, fatigue, kyphosis/scoliosis, muscle atrophy, osteoarthritis, osteopenia, thoracic spondylosis, left lobe liver lesion, morphine, anxiety, depression and insomnia. The patient's concomitant medications included acetaminophen, bisacodyl, calcium, concentrated red blood cells, darbepoetin alfa, diclofenac, diphenhydramine, esomeprazole, fentanyl, ferrous gluconate, gabapentin, hydrocodone and acetaminophen, hydrocortisone, magnesium hydroxide, methylphenidate, metoclopramide, misoprostol, sertraline, vinorelbine and zoledronic acid. This patient took his last study drug dose on 02 Sep 2006 and discontinued from the study on 05 Sep 2006. He discontinued the study because he withdrew consent. The reason for withdrawal of consent was not stated.

EN3267-005 Withdrawals – Double-Blind Treatment Phase

Patient No.: 523501
Case No(s).: Not applicable
Event(s): Withdrawn consent
Event Category(ies): Discontinuation due to withdrawn consent
Relationship(s) to Study Drug: Not applicable
This 61-year-old male took EN3267 as needed starting on 10 Aug 2006 for episodes of breakthrough cancer pain and was taking 100 to 400 µg sublingual tablets during the double-blind treatment phase of the study. The patient's medical history included pallor, dysphagia, chronic obstructive pulmonary disease, emphysema, lung cancer, pericardial effusion, pneumonitis, cardiac murmur, carotid calcifications, intermittent lower extremity edema, upper extremity edema, constipation, gastroesophageal reflux disease, intermittent nausea, vomiting, neuropathic pain, renal cysts, urinary difficulty, back pain, hyporeflexia, intermittent chest pain, shoulder pain, anemia, elevated platelets, elevated white blood cell, hyperkalemia, cervical spondylosis, compression fracture T12 and L1, degenerative joint disease, fatigue, kyphosis/scoliosis, muscle atrophy, osteoarthritis, osteopenia, thoracic spondylosis, left lobe liver lesion, morphine, anxiety, depression and insomnia. The patient's concomitant medications included acetaminophen, bisacodyl, calcium, concentrated red blood cells, darbepoetin alfa, diclofenac, diphenhydramine, esomeprazole, fentanyl, ferrous gluconate, gabapentin, hydrocodone and acetaminophen, hydrocortisone, magnesium hydroxide, methylphenidate, metoclopramide, misoprostol, sertraline, vinorelbine and zoledronic acid. This patient took his last study drug dose on 02 Sep 2006 and discontinued from the study on 05 Sep 2006. He discontinued the study because he withdrew consent. The reason for withdrawal of consent was not stated.

Eight of the above 13 narratives of subjects who withdrew consent during the open-label titration and double-blinded treatment phases did not state a reason for withdrawing consent, while two appeared to be related to lack of efficacy and one due to an AE.

9.6 Summary Tables of Adverse Events of the Mouth

Table 31: Oral Adverse Events in Single-dose with Naltrexone Studies in Healthy Subjects

	Dose			
System Organ Class Preferred Term	100 mcg (N=24) n (%)	400 mcg (N=78) n (%)	800 mcg (N=123) n (%)	1600 mcg (N=31) n (%)
At least one oral TEAE	0	4 (5.1)	5 (4.1)	0
Gastrointestinal disorders	0	3 (3.8)	3 (2.4)	0
Gingival pain	0	0	3 (2.4)	0
Dry mouth	0	1 (1.3)	0	0
Paraesthesia oral	0	1 (1.3)	0	0
Tongue discolouration	0	1 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders	0	2 (2.6)	1 (0.8)	0
Oropharyngeal pain	0	2 (2.6)	1 (0.8)	0
Infections and infestations	0	0	2 (1.6)	0
Pharyngitis	0	0	2 (1.6)	0

Source: Integrated Summary of Safety, Table 14.2.1, P. 3171 of 4367.

Table 32: Oral Adverse Events in Single-dose with Naltrexone Studies in Healthy Subjects by Dose Group

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=24) n (%)	>200 - <=400 mcg (N=78) n (%)	>400 mcg (N=124) n (%)	Overall (N=226) n (%)
At least one oral TEAE	0	4 (5.1)	5 (4.0)	9 (4.0)
Gastrointestinal disorders	0	3 (3.8)	3 (2.4)	6 (2.7)
Gingival pain	0	0	3 (2.4)	3 (1.3)
Dry mouth	0	1 (1.3)	0	1 (0.4)
Paraesthesia oral	0	1 (1.3)	0	1 (0.4)
Tongue discolouration	0	1 (1.3)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	2 (2.6)	1 (0.8)	3 (1.3)
Oropharyngeal pain	0	2 (2.6)	1 (0.8)	3 (1.3)
Infections and infestations	0	0	2 (1.6)	2 (0.9)
Pharyngitis	0	0	2 (1.6)	2 (0.9)

Source: Integrated Summary of Safety, Table 14.2.1.1, P. 3172 of 4367.

Table 33: Oral Adverse Events in Single-dose without Naltrexone Studies in Healthy Subjects

	Dose						
System Organ Class Preferred Term	50 mcg (N=21) n (%)	100 mcg (N=62) n (%)	150 mcg (N=20) n (%)	200 mcg (N=54) n (%)	300 mcg (N=6) n (%)	400 mcg (N=32) n (%)	800 mcg (N=12) n (%)
At least one oral TEAE	0	2 (3.2)	2 (10.0)	3 (5.6)	0	0	1 (8.3)
Respiratory, thoracic and mediastinal disorders	0	1 (1.6)	0	2 (3.7)	0	0	1 (8.3)
Oropharyngeal pain	0	1 (1.6)	0	0	0	0	1 (8.3)
Oropharyngeal blistering	0	0	0	1 (1.9)	0	0	0
Oropharyngeal swelling	0	0	0	1 (1.9)	0	0	0
Gastrointestinal disorders	0	1 (1.6)	1 (5.0)	2 (3.7)	0	0	0
Dry mouth	0	0	0	1 (1.9)	0	0	0
Hypoaesthesia oral	0	0	1 (5.0)	1 (1.9)	0	0	0
Paraesthesia oral	0	1 (1.6)	0	0	0	0	0
Infections and infestations	0	0	2 (10.0)	1 (1.9)	0	0	0
Pharyngitis	0	0	2 (10.0)	1 (1.9)	0	0	0

Source: Integrated Summary of Safety, Table 14.2.1.2, P. 3173 of 4367.

Table 34: Oral Adverse Events in Single-dose without Naltrexone Studies in Healthy Subjects by Pooled Dose Group

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=97) n (%)	>200 - <=400 mcg (N=38) n (%)	>400 mcg (N=12) n (%)	Overall (N=147) n (%)
At least one oral TEAE	6 (6.2)	0	1 (8.3)	7 (4.8)
Respiratory, thoracic and mediastinal disorders	3 (3.1)	0	1 (8.3)	4 (2.7)
Oropharyngeal pain	1 (1.0)	0	1 (8.3)	2 (1.4)
Oropharyngeal blistering	1 (1.0)	0	0	1 (0.7)
Oropharyngeal swelling	1 (1.0)	0	0	1 (0.7)
Gastrointestinal disorders	3 (3.1)	0	0	3 (2.0)
Dry mouth	1 (1.0)	0	0	1 (0.7)
Hypoaesthesia oral	1 (1.0)	0	0	1 (0.7)
Paraesthesia oral	1 (1.0)	0	0	1 (0.7)
Infections and infestations	2 (2.1)	0	0	2 (1.4)
Pharyngitis	2 (2.1)	0	0	2 (1.4)

Source: Integrated Summary of Safety, Table 14.2.2.1, P. 3174 of 4367.

Table 35: Oral Adverse Events in Multiple-dose Studies in Healthy Subjects

	Dose (1)					
System Organ Class Preferred Term	50 mcg (N=10) n (%)	100 mcg (N=21) n (%)	200 mcg (N=18) n (%)	300 mcg (N=6) n (%)	400 mcg (N=15) n (%)	800 mcg (N=12) n (%)
At least one oral TEAE	2 (20.0)	1 (4.8)	2 (11.1)	0	1 (6.7)	1 (8.3)
Gastrointestinal disorders	2 (20.0)	0	1 (5.6)	0	1 (6.7)	0
Dry mouth	1 (10.0)	0	1 (5.6)	0	0	0
Aphthous stomatitis	1 (10.0)	0	0	0	0	0
Cheilitis	0	0	0	0	1 (6.7)	0
Tongue haemorrhage	1 (10.0)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (4.8)	1 (5.6)	0	0	0
Oropharyngeal discomfort	0	1 (4.8)	0	0	0	0
Oropharyngeal pain	0	0	1 (5.6)	0	0	0
General disorders and administration site conditions	1 (10.0)	0	0	0	0	0
Application site irritation	1 (10.0)	0	0	0	0	0
Infections and infestations	0	0	0	0	0	1 (8.3)
Pharyngitis	0	0	0	0	0	1 (8.3)

Source: Integrated Summary of Safety, Table 14.2.3, P. 3175-6 of 4367.

Table 36: Oral Adverse Events in Multiple-dose Studies in Healthy Subjects by Pooled Dose Group

	Pooled Dose Group			
System Organ Class Preferred Term	<=200 mcg (N=49) n (%)	>200 - <=400 mcg (N=21) n (%)	>400 mcg (N=12) n (%)	Overall (N=82) n (%)
At least one oral TEAE	5 (10.2)	1 (4.8)	1 (8.3)	7 (8.5)
Gastrointestinal disorders	3 (6.1)	1 (4.8)	0	4 (4.9)
Dry mouth	2 (4.1)	0	0	2 (2.4)
Aphthous stomatitis	1 (2.0)	0	0	1 (1.2)
Cheilitis	0	1 (4.8)	0	1 (1.2)
Tongue haemorrhage	1 (2.0)	0	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	2 (4.1)	0	0	2 (2.4)
Oropharyngeal discomfort	1 (2.0)	0	0	1 (1.2)
Oropharyngeal pain	1 (2.0)	0	0	1 (1.2)
General disorders and administration site conditions	1 (2.0)	0	0	1 (1.2)
Application site irritation	1 (2.0)	0	0	1 (1.2)
Infections and infestations	0	0	1 (8.3)	1 (1.2)
Pharyngitis	0	0	1 (8.3)	1 (1.2)

Source: Integrated Summary of Safety, Table 14.2.3.1, P. 3177of 4367.

Table 37: Oral Adverse Events in Multiple-dose Studies in Cancer Patients

System Organ Class Preferred Term	Dose 100 mcg (N=22) n (%)	200 mcg (N=26) n (%)	300 mcg (N=58) n (%)	400 mcg (N=45) n (%)	600 mcg (N=66) n (%)	800 mcg (N=105) n (%)
At least one oral TEAE	3 (13.6)	4 (15.4)	7 (12.1)	12 (26.7)	18 (27.3)	20 (19.0)
Gastrointestinal disorders	3 (13.6)	4 (15.4)	6 (10.3)	7 (15.6)	15 (22.7)	14 (13.3)
Stomatitis	2 (9.1)	1 (3.8)	2 (3.4)	4 (8.9)	5 (7.6)	6 (5.7)
Dry mouth	1 (4.5)	0	3 (5.2)	2 (4.4)	5 (7.6)	0
Lip ulceration	0	0	1 (1.7)	1 (2.2)	1 (1.5)	1 (1.0)
Mouth ulceration	0	0	0	0	1 (1.5)	3 (2.9)
Cheilitis	0	1 (3.8)	0	0	1 (1.5)	1 (1.0)
Dental caries	0	0	0	0	0	3 (2.9)
Gingivitis	0	1 (3.8)	0	0	0	1 (1.0)
Tongue ulceration	0	0	0	0	1 (1.5)	1 (1.0)
Aphthous stomatitis	0	0	1 (1.7)	0	0	0
Chapped lips	0	0	0	0	1 (1.5)	0
Gingival bleeding	0	0	1 (1.7)	0	0	0
Gingival polyp	0	0	0	0	1 (1.5)	0
Gingival swelling	0	0	0	0	0	1 (1.0)
Hypoaesthesia oral	0	1 (3.8)	0	0	0	0
Lip blister	0	0	0	0	0	1 (1.0)
Oral discomfort	0	0	0	0	1 (1.5)	0
Oral disorder	0	1 (3.8)	0	0	0	0
Oral pain	0	0	0	0	1 (1.5)	0
Palatal disorder	1 (4.5)	0	0	0	0	0
Tongue disorder	0	0	0	1 (2.2)	0	0
Tongue dry	0	0	0	0	0	1 (1.0)
Infections and infestations	0	1 (3.8)	1 (1.7)	6 (13.3)	2 (3.0)	8 (7.6)
Tooth infection	0	0	1 (1.7)	1 (2.2)	1 (1.5)	1 (1.0)
Oropharyngeal candidiasis	0	0	0	0	0	3 (2.9)
Herpes simplex	0	0	0	1 (2.2)	0	1 (1.0)
Oral candidiasis	0	0	0	2 (4.4)	0	0
Pharyngitis	0	1 (3.8)	0	0	0	1 (1.0)
Pharyngitis streptococcal	0	0	0	1 (2.2)	0	1 (1.0)
Tooth abscess	0	0	0	1 (2.2)	1 (1.5)	0
Gingival infection	0	0	0	1 (2.2)	0	0
Pharyngitis bacterial	0	0	0	0	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	0	1 (3.8)	1 (1.7)	1 (2.2)	3 (4.5)	3 (2.9)
Oropharyngeal pain	0	1 (3.8)	1 (1.7)	1 (2.2)	3 (4.5)	2 (1.9)
Oropharyngeal blistering	0	0	0	0	0	1 (1.0)
Pharyngeal erythema	0	0	0	0	1 (1.5)	0
General disorders and administration site conditions	0	0	0	0	0	2 (1.9)
Mucosal inflammation	0	0	0	0	0	2 (1.9)
Injury, poisoning and procedural complications	0	0	0	1 (2.2)	0	1 (1.0)
Mouth injury	0	0	0	1 (2.2)	0	0
Tongue injury	0	0	0	0	0	1 (1.0)

Source: Integrated Summary of Safety, Table 14.2.5, P. 3180-2 of 4367.

Table 38: Oral Adverse Events in Multiple-dose Studies in Cancer Patients by Pooled Dose Group

System Organ Class Preferred Term	Pooled Dose Group <=200 mcg (N=45) n (%)	 >200 - <=400 mcg (N=98) n (%)	 >400 mcg (N=152) n (%)	 Overall (N=270) n (%)
At least one oral TEAE	7 (15.6)	19 (19.4)	38 (25.0)	64 (23.7)
Gastrointestinal disorders	7 (15.6)	13 (13.3)	29 (19.1)	49 (18.1)
Stomatitis	3 (6.7)	6 (6.1)	11 (7.2)	20 (7.4)
Dry mouth	1 (2.2)	5 (5.1)	5 (3.3)	11 (4.1)
Lip ulceration	0	2 (2.0)	2 (1.3)	4 (1.5)
Mouth ulceration	0	0	4 (2.6)	4 (1.5)
Cheilitis	1 (2.2)	0	2 (1.3)	3 (1.1)
Dental caries	0	0	3 (2.0)	3 (1.1)
Gingivitis	1 (2.2)	0	1 (0.7)	2 (0.7)
Tongue ulceration	0	0	2 (1.3)	2 (0.7)
Aphthous stomatitis	0	1 (1.0)	0	1 (0.4)
Chapped lips	0	0	1 (0.7)	1 (0.4)
Gingival bleeding	0	1 (1.0)	0	1 (0.4)
Gingival polyp	0	0	1 (0.7)	1 (0.4)
Gingival swelling	0	0	1 (0.7)	1 (0.4)
Hypoaesthesia oral	1 (2.2)	0	0	1 (0.4)
Lip blister	0	0	1 (0.7)	1 (0.4)
Oral discomfort	0	0	1 (0.7)	1 (0.4)
Oral disorder	1 (2.2)	0	0	1 (0.4)
Oral pain	0	0	1 (0.7)	1 (0.4)
Palatal disorder	1 (2.2)	0	0	1 (0.4)
Tongue disorder	0	1 (1.0)	0	1 (0.4)
Tongue dry	0	0	1 (0.7)	1 (0.4)
Infections and infestations	1 (2.2)	7 (7.1)	10 (6.6)	18 (6.7)
Tooth infection	0	2 (2.0)	2 (1.3)	4 (1.5)
Oropharyngeal candidiasis	0	0	3 (2.0)	3 (1.1)
Herpes simplex	0	1 (1.0)	1 (0.7)	2 (0.7)
Oral candidiasis	0	2 (2.0)	0	2 (0.7)
Pharyngitis	1 (2.2)	0	1 (0.7)	2 (0.7)
Pharyngitis streptococcal	0	1 (1.0)	1 (0.7)	2 (0.7)
Tooth abscess	0	1 (1.0)	1 (0.7)	2 (0.7)
Gingival infection	0	1 (1.0)	0	1 (0.4)
Pharyngitis bacterial	0	0	1 (0.7)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (2.2)	2 (2.0)	6 (3.9)	9 (3.3)
Oropharyngeal pain	1 (2.2)	2 (2.0)	5 (3.3)	8 (3.0)
Oropharyngeal blistering	0	0	1 (0.7)	1 (0.4)
Pharyngeal erythema	0	0	1 (0.7)	1 (0.4)
General disorders and administration site conditions	0	0	2 (1.3)	2 (0.7)
Mucosal inflammation	0	0	2 (1.3)	2 (0.7)
Injury, poisoning and procedural complications	0	1 (1.0)	1 (0.7)	2 (0.7)
Mouth injury	0	1 (1.0)	0	1 (0.4)
Tongue injury	0	0	1 (0.7)	1 (0.4)

Source: Integrated Summary of Safety, Table 14.2.5.1, P. 3183-5 of 4367.

Table 39: Oral Adverse Events in Multiple-dose Studies in Cancer Patients by Study Phase

System Organ Class Preferred Term	Completed Open-label Titration Phase (N=270) n(%)		Double-Blind Treatment Phase (N=66) (1) n (%)	Open-label Maintenance Phase (N=168) n (%)	Overall (N=270) n (%)
	No (N=96)	Yes (N=174)			
At least one oral TEAE	7 (7.3)	8 (4.6)	5 (7.6)	46 (27.4)	64 (23.7)
Gastrointestinal disorders	4 (4.2)	4 (2.3)	5 (7.6)	37 (22.0)	49 (18.1)
Stomatitis	0	1 (0.6)	2 (3.0)	17 (10.1)	20 (7.4)
Dry mouth	2 (2.1)	2 (1.1)	2 (3.0)	5 (3.0)	11 (4.1)
Lip ulceration	0	0	0	4 (2.4)	4 (1.5)
Mouth ulceration	0	0	0	4 (2.4)	4 (1.5)
Cheilitis	0	0	0	3 (1.8)	3 (1.1)
Dental caries	0	0	0	3 (1.8)	3 (1.1)
Gingivitis	0	0	0	2 (1.2)	2 (0.7)
Tongue ulceration	0	0	0	2 (1.2)	2 (0.7)
Aphthous stomatitis	0	0	0	1 (0.6)	1 (0.4)
Chapped lips	0	0	0	1 (0.6)	1 (0.4)
Gingival bleeding	0	0	0	1 (0.6)	1 (0.4)
Gingival polyp	0	0	0	1 (0.6)	1 (0.4)
Gingival swelling	0	0	0	1 (0.6)	1 (0.4)
Hypoaesthesia oral	0	0	0	1 (0.6)	1 (0.4)
Lip blister	0	0	0	1 (0.6)	1 (0.4)
Oral discomfort	0	1 (0.6)	0	0	1 (0.4)
Oral disorder	0	0	0	1 (0.6)	1 (0.4)
Oral pain	1 (1.0)	0	0	0	1 (0.4)
Gastrointestinal disorders (cont'd)					
Palatal disorder	0	0	1 (1.5)	0	1 (0.4)
Tongue disorder	1 (1.0)	0	0	0	1 (0.4)
Tongue dry	0	0	0	1 (0.6)	1 (0.4)
Infections and infestations	2 (2.1)	2 (1.1)	0	14 (8.3)	18 (6.7)
Tooth infection	0	1 (0.6)	0	3 (1.8)	4 (1.5)
Oropharyngeal candidiasis	1 (1.0)	0	0	2 (1.2)	3 (1.1)
Herpes simplex	1 (1.0)	0	0	1 (0.6)	2 (0.7)
Oral candidiasis	0	1 (0.6)	0	1 (0.6)	2 (0.7)
Pharyngitis	0	0	0	2 (1.2)	2 (0.7)
Pharyngitis streptococcal	0	0	0	2 (1.2)	2 (0.7)
Tooth abscess	0	0	0	2 (1.2)	2 (0.7)
Gingival infection	0	0	0	1 (0.6)	1 (0.4)
Pharyngitis bacterial	0	0	0	1 (0.6)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	2 (1.1)	0	6 (3.6)	9 (3.3)
Oropharyngeal pain	1 (1.0)	1 (0.6)	0	6 (3.6)	8 (3.0)
Oropharyngeal blistering	0	1 (0.6)	0	0	1 (0.4)
Pharyngeal erythema	0	0	0	1 (0.6)	1 (0.4)
General disorders and administration site conditions	0	0	0	2 (1.2)	2 (0.7)
Mucosal inflammation	0	0	0	2 (1.2)	2 (0.7)
Injury, poisoning and procedural complications	0	0	0	2 (1.2)	2 (0.7)
Mouth injury	0	0	0	1 (0.6)	1 (0.4)
Tongue injury	0	0	0	1 (0.6)	1 (0.4)

Source: Integrated Summary of Safety, Table 14.2.6, P. 3186-8 of 4367.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) (b) (4) tablets

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK PUCINO
03/16/2010

ROBERT B SHIBUYA
03/16/2010
I concur with Dr. Pucino's review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-510 **Applicant: ProStrakan** **Stamp Date: 05 August 2009**

Drug Name: Abstral (fentanyl) **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	√			505(b)(2) RLD: Actiq
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: EN3267-001, -012, -013 Study Title: Sample Size(s): ~10-48 Arms: Location in submission:	√			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 EN3267-005 Indication: Breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.	√			Supporting Study: SuF-002 (Phase 2).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			√	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			√	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			√	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? √

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Frank Rivin — 08/25/09
Reviewing Medical Officer — Date

[signature] — 8/26/09
Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK PUCINO
12/23/2010

ROBERT B SHIBUYA
12/23/2010
I concur with Dr. Pucino.