CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202788Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-788
Priority or Standard	Standard
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Division / Office	DAAAP/ODE2
Reviewer Name(s)	Luke Yip, MD
Review Completion Date	15 December 2011
Established Name	Fentanyl sublingual spray
(Proposed) Trade Name	
Therapeutic Class	Opioid analgesic
Applicant	Insys Therapeutics, Inc
Formulation(s)	Sublingual spray solution
Dosing Regimen	PRN, not to exceed 4 doses per 24 hours and not more frequent than 4 hours apart
Indication(s)	Breakthrough cancer pain
Intended Population(s)	Adult cancer patients receiving around the clock opioids with breakthrough pain

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that fentanyl sublingual spray (FSS) 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. The evaluation of safety was based on a safety database of approximately 350 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 FSS 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 period 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. This information was also not available for the open-label period of the study.

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. FSS 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 FSS use.

FSS will be the sixth oral transmucosal fentanyl product approved for the treatment of breakthrough cancer pain, joining Actiq, Fentora, Onsolis, Abstral, and Lazanda. All six product lines have some overlapping strengths. FSS is not bioequivalent to Actiq. 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 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 FSS outweigh the risks for the intended use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As a fentanyl-containing product for breakthrough cancer pain, FSS is subject to a Risk Evaluation and Mitigation Strategies (REMS) program.

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.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed indication for FSS, 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.

FSS is an opioid analgesic intended for oral sublingual administration. FSS is formulated as a clear, colorless solution that is available in six unit dosage strengths: 100 mcg (1 mg/mL), 200 mcg (2 mg/mL), 400 mcg (4 mg/mL), 600 mcg (6 mg/mL), or 800 mcg (8 mg/mL) fentanyl solution.

The proposed trade name, which has been found acceptable by Division of Medical Errors and Technical Support (DMETS), is SUBSYS, and the established name is fentanyl sublingual spray. 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 BTCP in cancer patients has consisted of treatment of the pain episode with a short-acting, immediate-release 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 immediate release oral opioids are approved for this indication.

There are currently five products (i.e., Actiq, Fentora, Onsolis, Abstral, and Lazanda) approved for BTCP in opioid-tolerant cancer patients.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently eight approved drug products (not including generic forms) in the United States containing the fentanyl moiety. Table 1 summarizes the important aspects of regulatory and post-marketing experience with these products. The overall adverse event profiles for all of the products are similar, and are typical of opioid effects (e.g., sedation, constipation, and respiratory depression). Table 1 also 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 iontophoretic transdermal system)	21-338	May 22, 2006	None	Never marketed due to safety issues regarding the device component
Fentora®	21-947	September 25, 2006	• Increased	• Off label use in opioid naïve patients

(fentanyl buccal tablet)			warnings regarding mis-prescribing to opioid naïve patients and improper dosing • RiskMAP was part of original approval	• 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 • REMS 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
Abstral® (fentanyl sublingual tablet)	22-510	January 7, 2010	• Increased warnings regarding mis-prescribing to opioid naïve patients and improper dosing • REMS 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
Lazanda® (fentanyl nasal spray)	22-569	June 30, 2011	• Increased warnings regarding mis-prescribing to opioid naïve patients and improper dosing • REMS 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, pruritus, 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. Other recognized risks associated with this class of drugs include abuse and addiction.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

FSS has been developed under IND 72,411.

Pre-IND meeting (25 August 2005)
The advice provided by the Division is summarized below:

- One adequate and well-controlled clinical trial would be sufficient to demonstrate efficacy of this sublingual drug delivery system.
- Evidence supporting proper dosing would be required for the claim of management of breakthrough cancer pain.

- "Taste Masking" will be necessary to ensure blinding between drug product and placebo.
- A safety database of at least 300 patients who used the to-be-marketed formulation and delivery device should be submitted at the time of NDA submission; 150 patients should be treated for 3 months and a significant proportion of the patients should be treated at the highest-to-be-marketed dose.
- The product should be tested under clinical conditions that may potentially alter the absorption of the product, i.e., stomatitis or drug/drug interactions with other co-incident oral preparations.
- Dosing guidelines for special populations (e.g., hepatic impairment and drug-drug interactions) should be developed.
- Conduct a single dose cross-over relative bioavailability with Actiq as the RLD, single dose PK: 200 vs. 400 vs. 600 vs. 800 mg (a single actuation (100 mL) from 2, 4, 6 and 8 mg/mL strengths).
- Contemplate how the PK of this drug might be altered with the consumption of alkaline or acidic beverages.

End-of-Phase 2 meeting (17 December 2007)
The advice provided by the Division is summarized below:

- A safety database of 300 patients is reasonable. This number should not include normal subjects who have received the investigational product during pharmacokinetic studies. Out of this total number of patients, 150 should have been treated for a minimum of 3 months with investigational product that is reasonably representative of the proposed to-be-marketed doses.
- (b) (4)
- Provide PK data of the drug product from 8-10 patients with mild stomatitis/mucositis in order to assess if membrane changes would lead to any changes in systemic absorption of the drug.
- Only clinically relevant information assessed with appropriate statistical methods will be included in the label. Secondary outcomes reflecting a variation of the primary outcome results will not be included in the product labeling.
- The term "opioid-treated" was not acceptable and the Sponsor should use the language of "opioid-tolerant."

Pre-NDA meeting (17 August 2010)
The advice provided by the Division is summarized below:

- Not required to conduct specific studies in patients with renal or hepatic insufficiency with your product.
- Three pharmacokinetic studies in healthy volunteers, one pharmacokinetic study in patients with or without mucositis, an efficacy and safety study in 130 patients, and a 3-month safety study in ≥150 patients will be sufficient to form the basis of a determination of product safety and efficacy barring any unanticipated safety

signals and presuming the results of your adequate and well controlled trial are confirmed.

- With respect to the pharmacokinetic study in patients with or without mucositis, include cancer patients with oral mucositis of grades 1, 2, 3, and 4. Alternatively, you may study cancer patients with grade 4 oral mucositis, and if there is no change in the PK in this group, patients with lower grade mucositis need not be studied.
- For the primary efficacy endpoint, a graphical representation of the data may be included in the label. (b) (4) .
- For secondary efficacy endpoints, only clinically relevant information (assessed with appropriate outcome measures and analyzed with appropriate statistical methods) will be included in the label.
- (b) (4)
- A Risk Evaluation and Mitigation Strategy (REMS) is required, and at a minimum will consist of Medication Guide, Elements to Assure Safe Use, Implementation System, Timetable for Submission of Assessments, address proper disposal of residual fentanyl product in the device, prescribing to opioid-tolerant patients only, appropriate dosing of these fentanyl products, and surveillance for misuse and abuse.
- The Agency is facilitating a meeting to discuss REMS for the class of transmucosal, immediate-release fentanyl (TIRF) products on 28 October 2010, and Insys has been invited.

2.6 Other Relevant Background Information

FSS is not approved in any other country; therefore there is no additional relevant background information.

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 numbers of patients enrolled and protocol violations. DSI found that, the inspections did not reveal any findings that suggested compromised data integrity. The overall inspection results indicate that the

study data were collected according to the study protocol and applicable good clinical practice regulations.

Please see Dr. John Lee's clinical inspection summary for details.

3.2 Compliance with Good Clinical Practices

The Applicant purports clinical studies were conducted in accordance with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), United States (US) 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects), US 21 CFR Part 56 (IRBs), and in accordance with the Declaration of Helsinki, Edinburgh 2004. The studies also conformed to any local Health Authority regulations.

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

Interested readers are referred to Dr. Julia Pinto's review for a complete discussion of CMC issues.

FSS is a sublingual spray form of a potent opioid analgesic, fentanyl (b) (4) intended for oral sublingual administration. It is designed to be sprayed on the floor of the mouth directly under the tongue. Fentanyl nasal spray is comprised of fentanyl (b) (4) in an alcohol/water solvent system. All of the excipients (i.e., menthol, xylitol, propylene glycol, absolute alcohol, and water) for the formulation are common ingredients in pharmaceutical preparations. The fentanyl solution is delivered using a unit dose system consists of an actuator, insert, spray pin, needle, stopper, glass vial, and vial holder (Figure 1). (b) (4)

Figure 1: FSS unit dose system

Source: 3.2.P.7 Container closure system, page 1/12 of the pdf

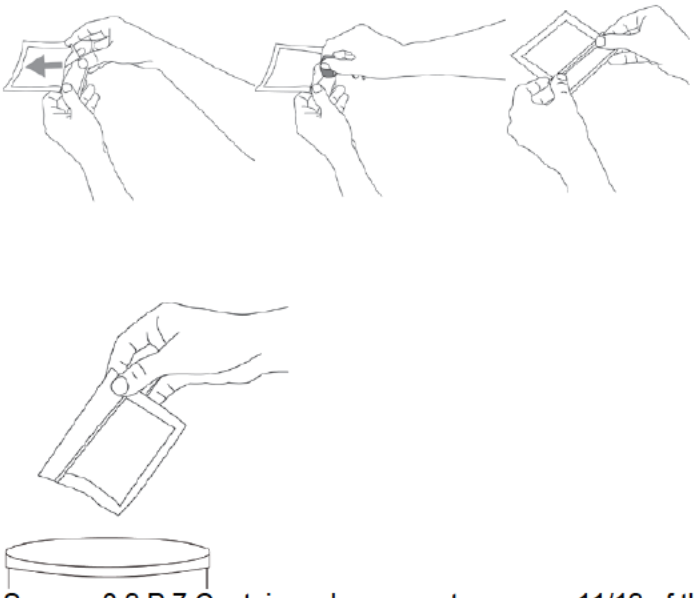
The unit dose spray devices are packaged in individually-sealed, (b) (4) protective blister packages that must be cut with scissors before the lid can be peeled back to remove the device for use.

FSS is packaged as a unit dose spray device. The fill volume is (b) (4) for each of the five strengths (i.e., 1, 2, 4, 6, and 8 mg/mL). The unit dose spray device is designed to deliver a total spray volume of (b) (4) of fentanyl solution containing fentanyl doses between 100 mcg and 800 mcg with (b) (4) residual. The 1200 mcg (2 x 600 mcg) and 1600 mcg (2 x 800 mcg) doses are delivered by actuating two unit dose spray devices. The Applicant's testing of devices actuated in a horizontal orientation perform in a manner similar to devices actuated in the vertical orientation.

For safe storage of FSS units, FSS Child Safety Kits will be available. The Child Safety Kit will consist of a portable pouch, a child-safety lock for securing the portable pouch, and a package of cabinet and drawer child safety latches.

For safe disposal of used FSS units, each carton configuration will contain heavy duty, (b) (4) plastic disposal bags in a quantity equal to the number of spray units in the carton along with a package insert and medication guide. The used spray device is to be inserted into a single bag and sealed with tape seal prior and then discarded in the household trash; see Figure 2 below.

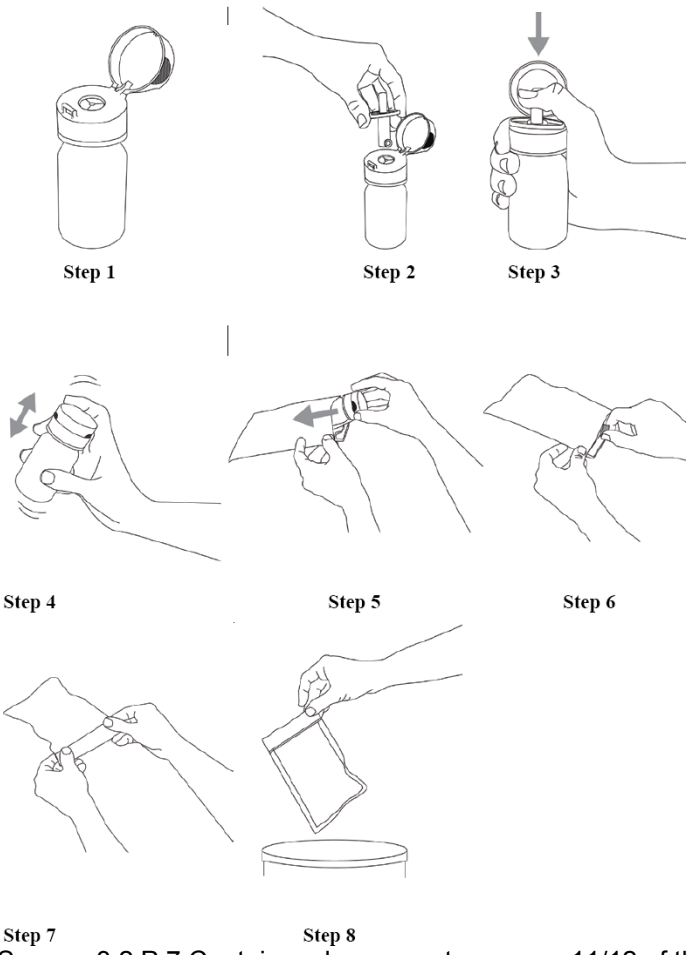
Figure 2: Disposal of a used FSS unit



Source: 3.2.P.7 Container closure system, page 11/12 of the pdf

For disposing of unused FSS unit dose spray device, a disposal high-density polyethylene (HDPE) bottle equipped with a flip-top cap fitted with a silicone insert that incorporates a child resistant removal feature of “press and turn at the same time” will be provided in a separate carton with each FSS prescription. Unused FSS unit dose spray devices are to be actuated inside the HDPE bottle. (b) (4) This amount of fentanyl is in approximately 28 FSS units of 8 mg/mL, which is the highest strength of this product. Once all unused units have been actuated into the HDPE bottle and the bottle has been closed and shaken, the bottle is inserted into the provided (b) (4) bag that is then closed by removing the adhesive tape and sealing it. The bag is then discarded into the household trash. Use of the disposal HDPE bottle is shown in Figure 3 below.

Figure 3: Use of disposal HDPE bottle



Source: 3.2.P.7 Container closure system, page 11/12 of the pdf

Recovery of fentanyl residual from unit dose spray device

Study CHP10010 was conducted to assess the amount of fentanyl that can be recovered from an actuated and disassembled FSS unit dose spray device under the following test conditions:

- Crushing: Up to six vials were crushed in a cotton dish cloth and the cloth was rinsed with 10 mL of water.
- Remove stopper: The stopper was removed using a nail, screw, paperclip, and a needle, and the stopper was rinsed with 10 mL of water.
- Tuberculin syringe: The stopper was pierced with a 26 gauge needle attached to a 1 mL tuberculin syringe to remove fentanyl that may be trapped underneath the stopper, and the syringe was rinsed with 10 mL of water.
- Boiling: A vial with a stopper was placed in 10 mL of 40% ethanol and the ethanol was boiled for 10 minutes. Another vial with a stopper was placed in 10 mL of water and the water was boiled for 10 minutes.

- Open flame: A vial with a stopper was held over candle flame for 10 minutes. The stopper was immediately ejected from the vial. The vial and stopper were rinsed with 5 mL of water. The actuator portion from the disassembled device was held over an open flame of the candle. The actuator immediately caught fire and was not analyzed further.
- Microwave: An actuated spray device was placed in a 1000 Watt microwave oven for heating on full power for 5, 10, and 30 minutes. The device was then disassembled and its actuator and vial were separately rinsed in water or ethanol. One device that was microwaved for 10 minutes and one device that was microwaved for 30 minutes melted.
- Vacuum simulating suction by mouth: 20 actuated devices were placed in vacuum oven with nozzle facing downward on a paper towel for 5 minutes. The amount of vacuum studied was equivalent to 20.7 mm Hg based on vacuum used for breast pumps and 8.9 mm Hg based on suction by a child.

All the studies utilized the highest strength of the FSS unit dose spray device (i.e., 8 mg/mL) to represent the worst case scenario. Table 2 summarizes the results of the test conditions. The quantity of fentanyl recovered under test conditions was between (b) (4) (0 to 45% of the residual (b) (4)).

Table 2: Recovery of fentanyl from unit dose spray device

Test condition	Fentanyl recovered	Percent of residual*
Crushing	(b) (4)	0.0 – **7.5%
Remove stopper	(b) (4)	2.6 – 10.7%
Tuberculin syringe	(b) (4)	31.6 – 42.7%
Boiling	(b) (4)	7.1%
Open flame	(b) (4)	9.6%
Microwave	(b) (4)	6.8 – 21.6%
Vacuum suction	(b) (4)	15.3 – 36.7%

*Residual = (b) (4)
**Based on residual for 6 unit dose spray devices

Study CHP10014 was conducted to assess the amount of fentanyl that can be extracted from activated (b) (4) after 28 FSS units of 8 mg/mL ((b) (4) mg of fentanyl), the worse case scenario, have been actuated inside a HDPE bottle (b) (4) The extraction studies were conducted using ethanol, methanol, isopropanol, acetone, and ethyl acetate, at various times (1 to 12 hours), at room temperature and after heating (50 to 90 degrees Celsius) and agitation, and under neutral (water), acidic (hydrochloric acid), and basic (sodium hydroxide) pH conditions. The amount of extractable fentanyl ranged from (b) (4) mcg (1.2% of the total fentanyl). The test conditions that allowed for extracting the largest amount of fentanyl from (b) (4) in descending order were: agitation with ethanol at room temperature for one hour ((b) (4) mcg, 1.2%), agitation with isopropanol at room temperature for one hour (b) (4) mcg, 1.2%), agitation with acetone at room temperature for one hour (b) (4)

1.0%), agitation with ethyl acetate at room temperature for one hour (b) (4) mcg, 0.5%), agitation with methanol at room temperature for one hour ((b) (4) mcg, 0.4%), agitation with water at room temperature for one hour (b) (4) mcg, 0.04%), and agitation with hydrochloric acid at room temperature for one hour (b) (4) mcg, 0.03%). Fentanyl that had been adsorbed onto activated (b) (4) does not appear to be extractable by water, methanol or hydrochloric acid when heated. The pH of a solution did not appear to enhance the extractability of fentanyl.

4.2 Clinical Microbiology

Interested readers are referred to Dr. Bryan Riley's review for a complete product quality microbiology review.

The Clinical Microbiology review team found that the drug product microbial limits acceptance criteria for total aerobic count and total yeast and mold are (b) (4) than the suggested acceptance criteria for an oral liquid product. However, the administered dose of the drug product is small (b) (4) so that the difference in acceptance criteria is not a concern from a product quality microbiology standpoint.

The current policy of Clinical Microbiology is that aqueous drug products should have controls in place to ensure the absence of *Burkholderia cepacia*. The drug product specification does not include a test for *B. cepacia*. However, this does not appear to be a concern because the drug product composition (b) (4)

4.3 Preclinical Pharmacology/Toxicology

Interested readers are referred to Dr. Elizabeth Bolan's review for a complete discussion of the preclinical development of FSS.

The Applicant did not submit any nonclinical pharmacology studies with this NDA.

All of the excipients (i.e., menthol, xylitol, propylene glycol, absolute alcohol, and water) for the formulation are below previously approved levels and are considered acceptable.

The specifications for drug substance impurities are acceptable. As for the drug product specifications, the Applicant has identified (b) (4) as a fentanyl-related degradant. The FDA Informatics and Computational Safety Analysis Staff (ICSAS) predicts (b) (4) will be positive for Salmonella mutagenesis based solely on a moderately positive call by one of four programs used to predict mutagenicity. The Pharmacology/Toxicology team will consider (b) (4) to be potentially mutagenic and have requested, and the Applicant has agreed to conduct, an Ames Assay with (b) (4) in order to definitively define the potential for mutagenicity. The Applicant submitted the results of the Ames Assay with (b) (4) during the NDA review cycle, and it as negative.

4.4 Clinical Pharmacology

Interested readers are referred to Dr. Wei Qiu's review for a complete discussion of the clinical pharmacology aspects of FSS.

4.4.1 Mechanism of Action

Fentanyl is a full 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.

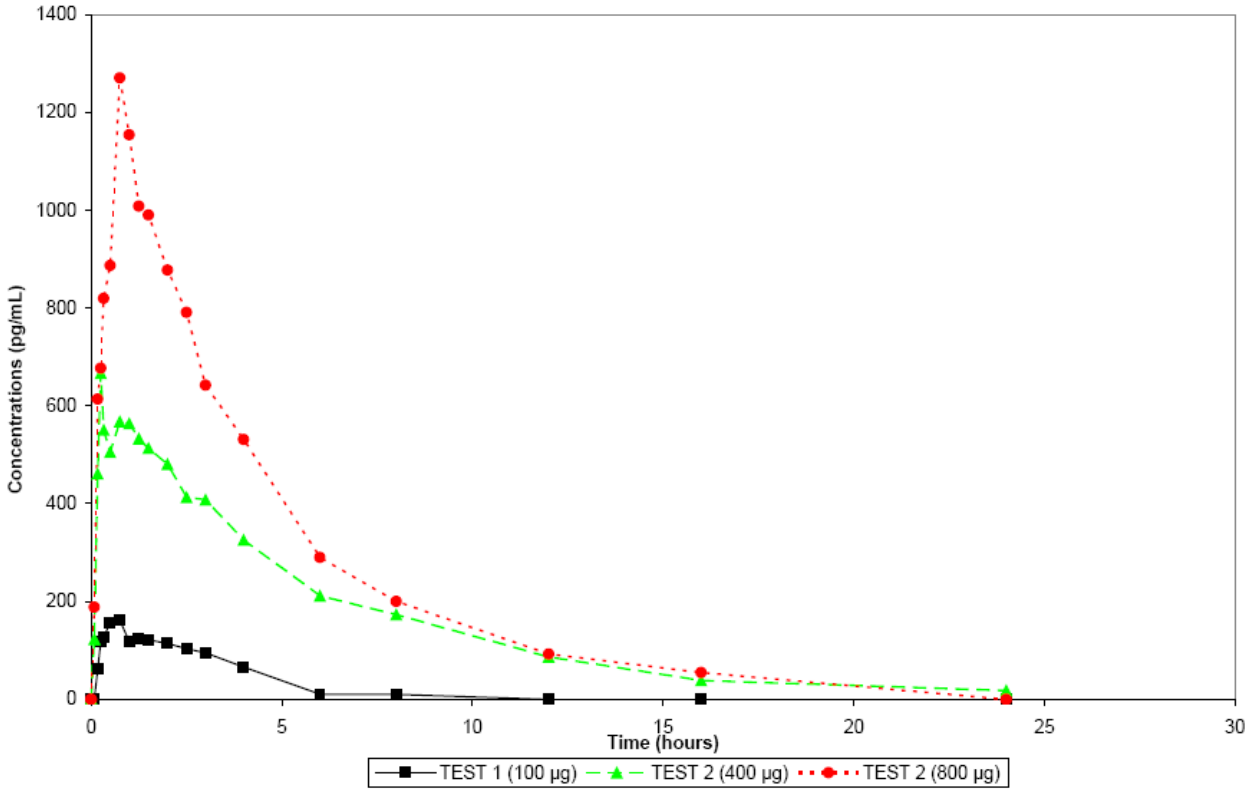
4.4.2 Pharmacodynamics

There were no pharmacodynamic studies conducted with FSS.

4.4.3 Pharmacokinetics

FNY-P4-270 was a pilot study in which a single ascending FSS dose (100 mcg, 400 mcg, and 800 mcg) was administered to healthy subjects under fasted conditions. The summary data is shown in Figure 4 and Table 3. The pharmacokinetic parameters appeared to be dose proportional.

Figure 4: Mean fentanyl concentration-time profiles



Source: FNY-P4-270 report, page 63/346 of the pdf

Table 3: FSS pharmacokinetics over dose range 100 mcg to 800 mcg

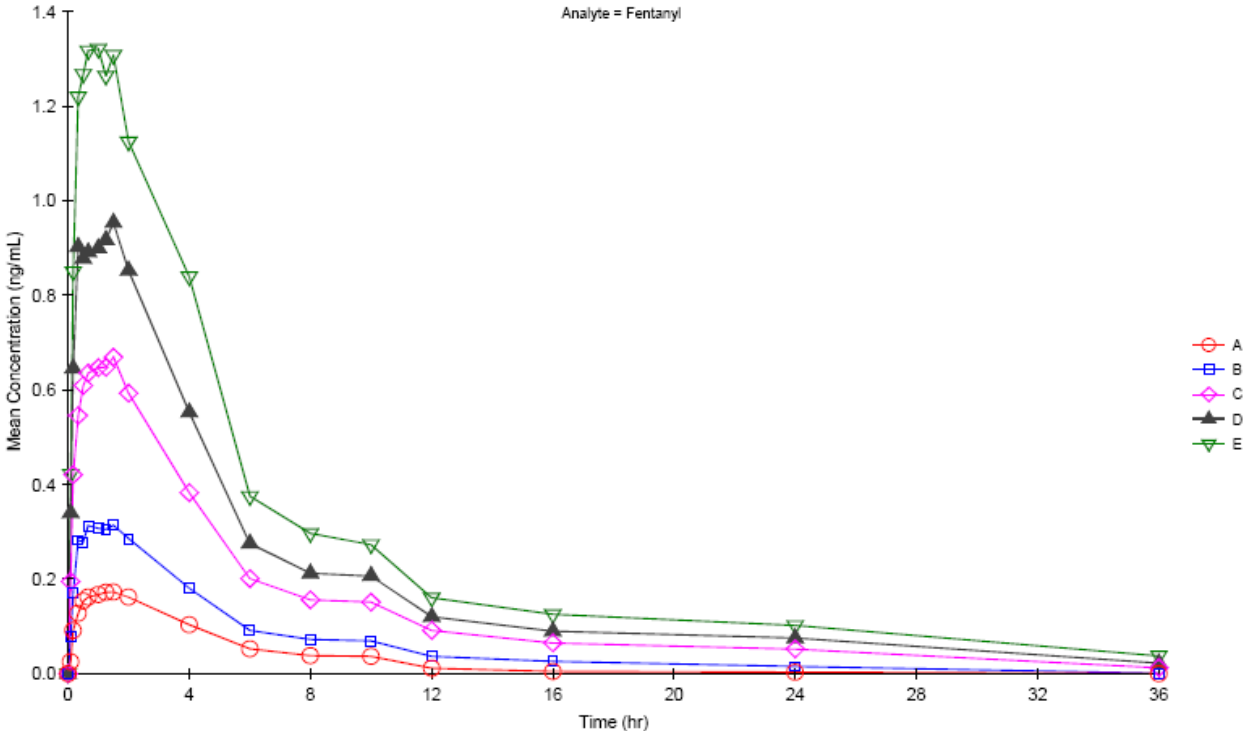
	FSS 100 mcg		FSS 400 mcg		FSS 800 mcg	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Tmax (h)	0.50	29.7	0.50	61.3	0.75	0.0
Cmax (pg/mL)	172.0	27.1	708.0	50.2	1270.0	37.7
AUC_{inf} (pg•h/mL)	817.9	36.1	4242.6	57.6	5726.8	28.8
T½ (h)	3.70	30.4	5.20	45.8	3.89	0.9

Source: Modified from FNY-P4-270 report, page 60/396 of the pdf
CV=coefficient of variation

Study INS-06-004 was conducted to assess the pharmacokinetics of fentanyl following a single FSS dose (100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg) in naltrexone-blocked healthy subjects under fasted conditions. Absorption of fentanyl from FSS is mainly through the oral mucosa. The summary data is shown in Figure 5 and Table 4. In Figure 5, the mean Cmax fentanyl concentrations following FSS 400, 600, and 800 mcg dosing appear lower than the values in Table 4. An explanation is the values in Figure 5 are the mean Cmax fentanyl concentration for all the subjects at a given time, whereas the values in Table 4 are the mean Cmax fentanyl concentration for all the subjects. The

Cmax and AUC values were approximately dose-proportional over the dose range 100 mcg to 800 mcg. The median Tmax values ranged from 40 to 75 minutes. Following Cmax, plasma fentanyl concentrations declined with mean apparent terminal elimination half-life values ranging from 5 to 12 hours.

Figure 5: Mean fentanyl concentration-time profiles after FSS 100 mcg (A), 200 mcg (B), 400 mcg (C), 600 mcg (D), and 800 mcg (E)



Source: INS-06-004 report, page 50/3150 of the pdf

Table 4: FSS pharmacokinetics over dose range 100 mcg to 800 mcg

FSS (mcg)	100	200	400	600	800
*Tmax (h)	1.25 (0.17, 2.05)	1.25 (0.17, 2.03)	1.00 (0.17, 2.03)	0.67 (0.08, 2.00)	0.69 (0.17, 4.00)
**Cmax (ng/mL)	0.202 (0.057)	0.378 (0.112)	0.800 (0.221)	1.17 (0.378)	1.61 (0.601)
**AUC_{last} (ng•h/mL)	0.978 (0.487)	1.985 (0.812)	4.643 (2.068)	6.682 (2.169)	9.450 (3.460)
**AUC_{inf} (ng•h/mL)	1.245 (0.670)	2.475 (1.15)	5.342 (2.359)	7.446 (2.348)	10.38 (3.697)
**T½ (h)	5.25 (4.72)	8.45 (6.58)	11.03 (6.86)	10.64 (4.44)	11.99 (3.86)

Source: Modified from INS-06-004 report, page 58-59/3150 of the pdf
*median (min, max)
**mean (SD)

Study INS-06-003 was conducted to assess the relative bioavailability of a single FSS 400 mcg dose to an oral transmucosal fentanyl citrate lozenge Actiq 400 mcg in naltrexone-blocked healthy subjects under fasted conditions. The summary data is shown in Table 5 and Table 6. FSS was not bioequivalent to Actiq. The mean absolute bioavailability of FSS was 72% to 76% whereas Actiq was 51% to 54% (Table 5). The geometric mean relative bioavailability was 34% higher in Cmax and 36% higher in AUC values than Actiq (Table 6).

Table 5: Bioavailability of fentanyl after FSS and Actiq administration

Treatment	AUC_{last}		AUC_{inf}	
	Mean (SD)	CV (%)	Mean (SD)	CV (%)
FSS 400 mcg	0.721 (0.199)	27.59	0.756 (0.212)	28.02
Actiq 400 mcg	0.540 (0.135)	25.08	0.511 (0.0973)	19.05

Source: Modified from INS-06-003 report, page 40/1911 of the pdf
CV=coefficient of variation

Table 6: Bioavailability of fentanyl after FSS 400 mcg (Treatment A) and Actiq 400 mcg (Treatment B) administration

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	0.7865	0.5884	133.67	119.67	149.31	0.9527	20.85
$ln(AUC_{last})$	4.6392	3.4767	133.44	121.47	146.58	0.9859	17.65
$ln(AUC_{inf})$	5.5080	4.0420	136.27	121.21	153.20	0.9341	17.06

[a] Geometric Mean for Treatment A (Test) and Treatment B (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Source: INS-06-003 report, page 40/1911 of the pdf

Study INS-06-004 was conducted to assess the effect of temperature and pH in the oral cavity on the relative bioavailability of FSS. The temperature in the oral cavity was manipulated using either water cooled to refrigerated ice water temperature or water heated to hot coffee or tea temperature. The pH in the oral cavity was manipulated using either carbonated beverage (i.e., Coca-Cola or Sprite) for low pH condition or aqueous solution of ½ teaspoon sodium bicarbonate in 4 ounces of room temperature water for the high pH condition. A single dose FSS 200 mcg was administered to

naltrexone-blocked healthy subjects under fasted conditions. The summary data is shown in Table 7. Cold and hot beverage did not significantly effect the pharmacokinetic parameters. High pH beverage increased fentanyl Cmax and AUC values by approximately 20%, whereas low pH beverage did not significantly effect the pharmacokinetic parameters.

Table 7: Effect of temperature and pH on FSS pharmacokinetics

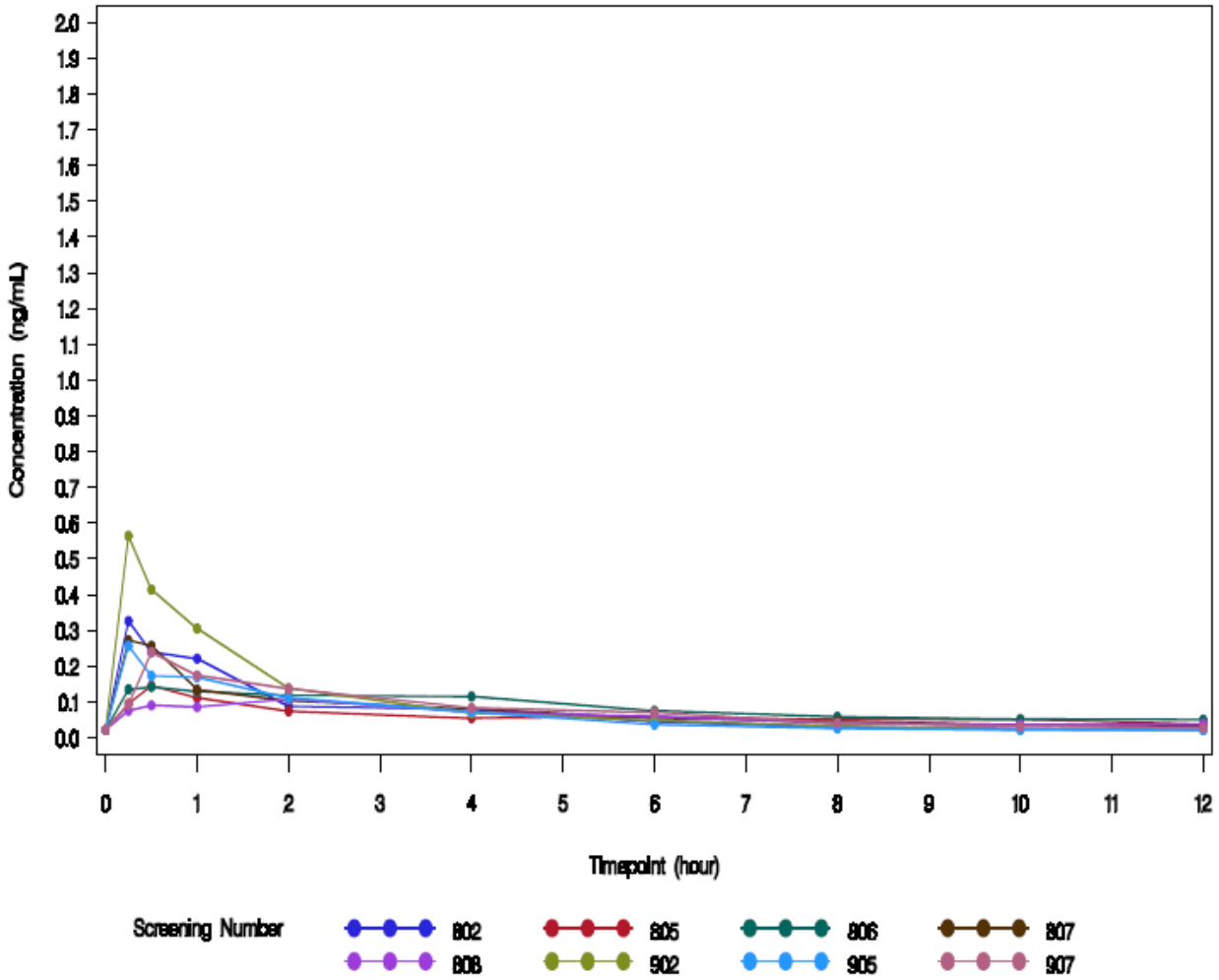
PK Parameter	Cold Beverage	Hot Beverage	No Pretreatment	Cold/No pretreatment ratio (90% CI)	Hot/No pretreatment ratio (90% CI)
*Tmax (h)	1.22 (0.17, 1.50)	1.50 (0.33, 4.00)	1.38 (0.33, 2.00)	---	---
**Cmax (ng/mL)	0.325 (0.098)	0.324 (0.128)	0.336 (0.088)	100.8 (83.07, 120.58)	96.88 (81.79, 114.76)
**AUC_{last} (ng•h/mL)	1.983 (0.657)	2.005 (0.689)	1.997 (0.703)	94.78 (75.95, 118.29)	97.27 (83.71, 113.03)
**AUC_{inf} (ng•h/mL)	2.468 (1.076)	2.459 (0.912)	2.427 (0.983)	92.23 (73.38, 115.93)	101.25 (85.87, 119.38)
	Low pH Beverage	High pH Beverage	No Pretreatment	Low pH/No pretreatment ratio (90% CI)	High pH/No pretreatment ratio (90% CI)
*Tmax (h)	2.00 (1.00, 2.07)	1.00 (0.33, 2.00)	1.38 (0.33, 2.00)	---	---
**Cmax (ng/mL)	0.291 (0.108)	0.409 (0.161)	0.336 (0.088)	83.26 (70.81, 97.90)	123.08 (107.98, 140.29)
**AUC_{last} (ng•h/mL)	1.833 (1.004)	2.316 (1.021)	1.997 (0.703)	91.93 (81.70, 103.44)	119.08 (101.60, 139.58)
**AUC_{inf} (ng•h/mL)	2.368 (1.341)	2.746 (1.274)	2.427 (0.983)	95.68 (84.39, 108.49)	118.56 (104.16, 134.95)

Source: Modified from INS-06-004 report, page 102-106/3150 of the pdf
*median (min, max)
**mean (SD)
Cold beverage: Water cooled to temperature of refrigerated ice water
Hot beverage: Water heated to temperature of hot coffee or tea
Low pH beverage: Carbonated beverage (i.e., Coca-Cola or Sprite)
High pH beverage: Aqueous solution of ½ teaspoon sodium bicarbonate in 4 ounces of room temperature water

Study INS-09-011 was conducted to assess the effect of mucositis on the pharmacokinetics of FSS. A single dose of FSS 100 mcg was administered to opioid-tolerant cancer patients without and with mucositis. The summary data are shown in Figure 6, Figure 7, and Table 8. Patients with Grade 1 mucositis have a 73% increase in Cmax and a 52% increase in AUC values compared with patients without mucositis; see

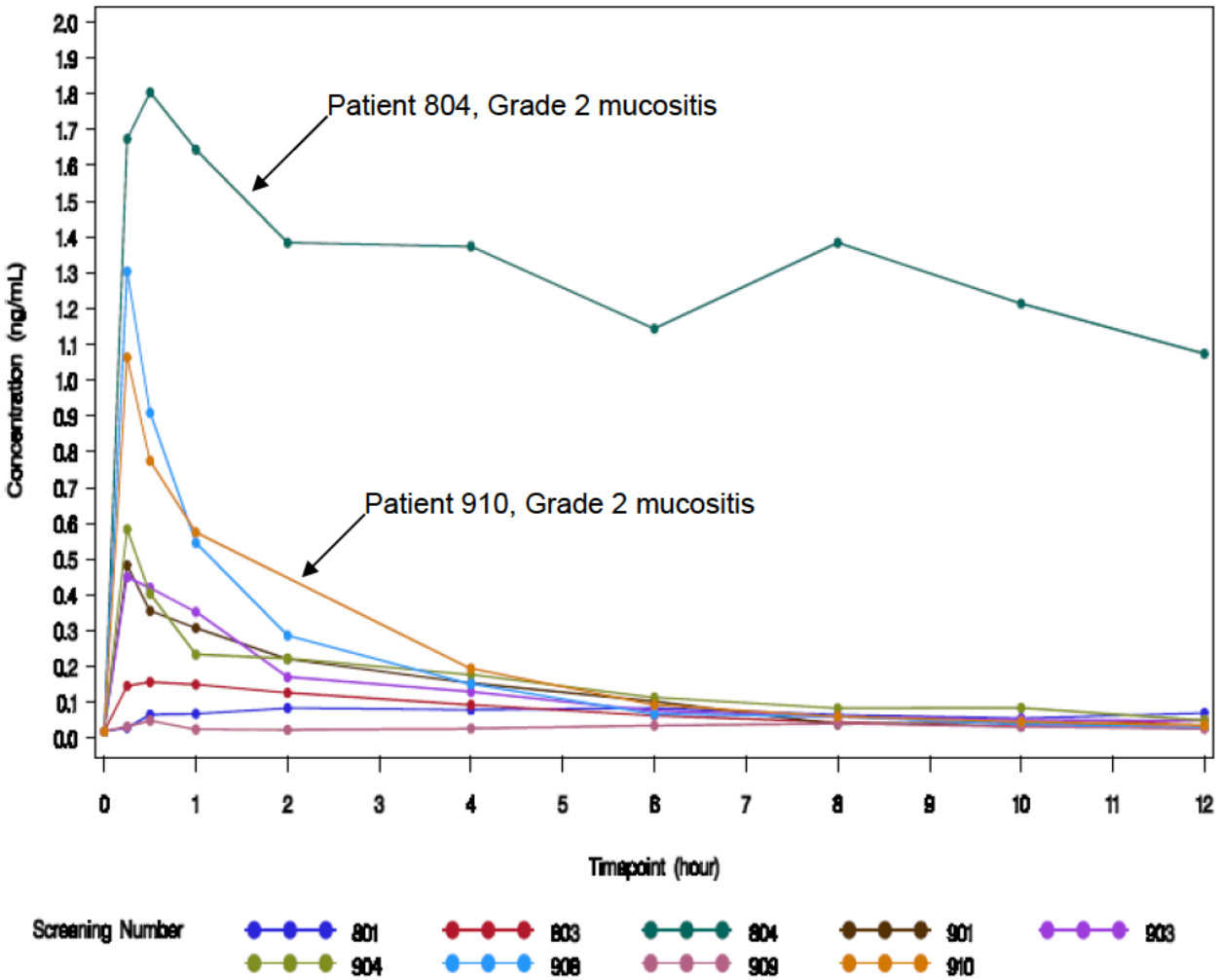
Table 8. There were two patients with Grade 2 mucositis, Patient 804 and Patient 910, and they achieved a higher fentanyl exposure than patients with Grade 1 or without mucositis; see Figure 7 and Table 8. Patient 804 had a 7-fold higher Cmax and 17-fold higher AUC values compared with patients without mucositis. Patient 910 had a 4-fold higher Cmax and 3-fold higher AUC values compared with patients without mucositis. It appears that patients with mucositis may achieve a higher fentanyl exposure following FSS use. This information should be included in the product label to caution prescribers and users of this product that use of FSS in the presence of mucositis may result in a higher exposure level to fentanyl.

Figure 6: Fentanyl concentration – patients without mucositis



Source: INS-09-011 report, page 49/614 of the pdf

Figure 7: Fentanyl concentration – patients with mucositis



Source: Modified from INS-06-003 report, page 49/614 of the pdf

Table 8: Fentanyl pharmacokinetics in patients without and with mucositis

Mucositis	None (N=8)	Grade 1 (N=7)	Grade 1 and 2 (N=9)	Grade 2 Patient 804	Grade 2 Patient 910
*Tmax (h)	0.38 (0.25, 2.00)	0.25 (0.25, 2.00)	0.25 (0.25, 2.00)	0.5	0.25
**Cmax (ng/mL)	0.26 (0.15)	0.45 (0.43)	0.67 (0.60)	1.81	1.07
**AUC_{last} (ng•h/mL)	0.91 (0.13)	1.38 (0.62)	3.11 (4.80)	15.78	2.56

*median (min, max)
**mean (SD)

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 9: Summary of Clinical Studies Supporting Findings of Efficacy and Safety

Study	Objective	Design	Treatment dosing	Number of patients	Duration
FNY-P4-270	Determine PK, safety and tolerability of FSS under fasting conditions	Single-blind, placebo controlled, single-dose, sequential ascending dose with 13-15 day washout	FSS 100, 400, 800 mcg or placebo	Enrolled: 9 healthy males Treated: 9 Completed: 5 Analyzed: 6	Single dose
INS-06-003	Compare absorption and bioavailability of FSS to Actiq and IV fentanyl citrate under fasting conditions	Open-label, randomized, single-dose, 3 period, 3 treatment crossover study with 7 day washout; *naltrexone* block	FSS 400 mcg, Actiq 400 mcg, IV fentanyl citrate 100 mcg; naltrexone 50 mg	Enrolled: 40 healthy subjects Treated: 40 Completed: 29 Analyzed: 21	Single dose, 3 days
INS-06-004	Part A: Comparative PK study of 5 different doses of FSS under fasted conditions Part B: Effect of temperature and pH of oral cavity on PK parameters of FSS	Open-label study Part A: Single-dose, 5 treatment, 5 sequence, 5 period crossover; *naltrexone* block Part B: Single-dose, 5 treatment, 2 sequence, 5 period crossover	Part A: FSS 100, 200, 400, 600, 800 mcg; naltrexone 50 mg Part B: FSS 200 mcg; naltrexone 50 mg	Enrolled: 67 healthy subjects Part A Completed: 45 Analyzed: 38 Part B Completed: 14 Analyzed: 11	Single dose, 5 days
INS-09-011	Safety, tolerability, and absorption/distribution kinetics of FSS in cancer patients with or without mucositis	Open-label, single-dose study	FSS 100 mcg	Opioid-tolerant cancer patients: 18 Mucositis Enrolled: 9 Completed: 9 Analyzed: 9 No mucositis Enrolled: 9 Completed: 9 Analyzed: 8	Single dose
INS-05-001	Efficacy and safety of FSS for the treatment of	Randomized, double-blind, placebo-controlled,	FSS 100, 200, 400, 600, 800, 1200, 1600 mcg or placebo	Opioid-tolerant cancer patients with	Up to 52 days

	breakthrough cancer pain in opioid-tolerant patients	multicenter study	Titration: Single dose until adequate pain relief achieved for 2 consecutive pain episodes; re-dose allowed with single dose within 30 minutes Double-blind: Single dose up to 2 pain episodes per day, for total of 10 pain episodes	breakthrough cancer pain Enrolled: 161 Titration: 130 Double-blind: 98 Completed: 95 Rolled over to INS-06-007: 90	
INS-06-007	Safety of FSS for the treatment of breakthrough cancer pain in opioid-tolerant patients	Open-label, multi-center study	FSS 100, 200, 400, 600, 800, 1200, 1600 mcg Titration: Single dose until adequate pain relief achieved for 2 consecutive pain episodes; re-dose allowed with single-dose within 30 minutes Maintenance: Single dose; up to 4 breakthrough pain episodes per day	Opioid-tolerant cancer patients with breakthrough cancer pain Enrolled: 261 Titration: 229 Completed: 179 Maintenance: 269 (179+90 rolled over from INS-05-001)	90-111 days

Source: Modified from FSS NDA Tabular Listing of All Clinical Studies, page 1-5 of pdf.

5.2 Review Strategy

For this 505(b)(2) application, the Applicant submitted a single adequate and well-controlled efficacy study (INS-05-001). The Applicant also relied on the Agency's prior findings of efficacy for Actiq (oral transmucosal fentanyl citrate).

Dr. Yan Zhou of the Division of Biometrics 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 INS-05-001.

5.3 Discussion of Individual Studies/Clinical Trials

The efficacy for NDA 202-788 is supported by a single adequate and well-controlled clinical trial, INS-05-001 in addition to reference to the Agency's prior finding of analgesic efficacy for Actiq. The intended use of Actiq, the pharmacokinetic profile, and the route of administration are sufficiently similar to provide support for efficacy of FSS. Study INS-05-001 was designed comparably to the efficacy study used for approval of Actiq, a double-blind, placebo-controlled, crossover study, a design used successfully for products intended for the treatment of breakthrough pain in opioid tolerant adult patients with pain due to cancer.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

FSS is indicated for the management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking FENTANYL SUBLINGUAL SPRAY.

6.1.1 Methods

The efficacy for NDA 202-788 is supported by a single adequate and well-controlled clinical trial, protocol INS-05-001 in addition to reference to the Agency's prior finding of analgesic efficacy for fentanyl. The Applicant submitted five amendments to the NDA as shown in Table 10. Three of the amendments were implemented prior to the first patient enrollment. This protocol review reflects the original protocol with incorporation of the first three amendments. Protocol amendments implemented after the first patient enrollment are indicated at the end of the respective protocol sections in *italics*.

Table 10: Protocol Amendments

Submission	Date
Original protocol	20 June 2007
Amendment 1	04 September 2007
Amendment 2	18 September 2007
Amendment 2.1	28 September 2007 (V2.1)

First patient enrolled: 18 October 2007	
Amendment 3	06 December 2007
Amendment 4	04 April 2008
Data lock: 22 February 2010	

Title
"A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain."

Objectives

- Primary objective: "…assess the efficacy of Fentanyl SL Spray for the treatment of breakthrough cancer pain in opioid-treated subjects."

- Secondary objective: "…evaluate the safety of Fentanyl SL Spray in these opioid-treated subjects." and "…assess the subject's satisfaction with treatment medication."

Amendment 4 (04 April 2008): The term "opioid-treated" was to have been changed back to "opioid-tolerant" as it appeared in the original protocol.

Study Design
This was to have been a randomized, double-blind, placebo-controlled, crossover, efficacy and safety trial conducted in approximately 35 centers in the United States.

Duration
The study was to have consisted of a Screening Visit before enrollment, an open-label, dose-titration period of up to 21 days, and a double-blind, placebo-controlled crossover period of up to 21 days. The maximum study duration for individual patients was to have been six weeks (42 days).

Amendment 4 (04 April 2008): The duration of the open-label, dose-titration period and the double-blind, placebo-controlled crossover period was to have been modified from up to 21 days to up to 26 days, and the maximum study duration for individual patients was to have been modified from 42 days to 52 days, accordingly.

Sample Size
One hundred thirty patients with cancer-related pain and frequent episodes of acute breakthrough cancer pain (BTCP) superimposed on their chronic pain were to have been enrolled into the titration portion of the study in order that approximately 90 patients would complete the double-blind portion of the study.

Inclusion Criteria
Patients were to be included in the study if they met the following key criteria:

1. Male or non-pregnant, non-lactating female age 18 years and older; female of childbearing potential must have a negative serum pregnancy test, not breast feeding, and agree to practice reliable form of contraception
2. A diagnosis of cancer and with persistent cancer pain or its treatment of moderate or less intensity in the 24 hours prior to assessment by a verbal rating scale at the Screening Visit
3. Taking at least 25 mcg of transdermal fentanyl per hour or 60 mg of oral morphine per day, 30 mg of oxycodone per day, 8 mg of oral hydromorphone or equivalent per day for at least one week for cancer-related pain as regular, 24-hour medication for underlying persistent cancer pain
4. Experiences on average one to four episodes of BTCP per day and be at least partially controlled by supplemental medication of at least 5 mg immediate-release morphine or an equivalent short-acting opioid (e.g., oxycodone, hydrocodone, or acetaminophen with codeine)
5. Be able to evaluate and record pain relief, assess medication performance and record AEs

Amendment 4 (04 April 2008): Experiences on average 1 to 4 episodes of BTCP per day were to have been modified to experiences on an average 1 to 4 episodes of BTCP per day over the previous 7 days.

Exclusion Criteria
Patients were to be excluded from participating in the study if they met any of the following key exclusion criteria:

1. Current use of commercially available short-acting fentanyl for breakthrough pain or used methadone within 14 days of Screening Visit
2. Rapidly increasing or uncontrolled pain
3. Uncontrolled hypertension (i.e., systolic > 180 mmHg or diastolic > 90 mmHg) despite antihypertensive therapy, or has a history of hypertensive crisis within the past two years
4. Brain metastases with signs or symptoms of increased intracranial pressure
5. Use of MAOIs within 14 days of the Screening Visit
6. Transient ischemic attacks, neural vascular disease, stroke, or cerebral aneurysms within the past two years
7. Diagnosis of sleep apnea
8. Painful erythema, edema or ulcers under the tongue
9. Serum creatinine, ALT or AST more than three times the upper limit of normal

Amendment 3 (06 December 2007):

- *Use of methadone within 14 days of Screening Visit was to have been no longer an exclusion criterion.*
- *"Diagnosis of sleep apnea" was to have been changed to "clinically uncontrolled sleep apnea."*

- *Serum creatinine, ALT or AST > 3 times the upper limit of normal was to have been no longer an exclusion criterion.*

Amendment 4 (04 April 2008): The use of short-acting fentanyl criterion was to have been modified to patients on Actiq or Fentora were eligible if they had a 7 day washout.

Treatments
FSS were to have been dispensed in unit doses in specifically designed unit dose spray devices. The fill volume of each unit dose spray device was to have been 130 mcL of fentanyl solution. Each single spray dose was to have delivered 100 mcL of fentanyl solution containing 100, 200, 400, 600, or 800 mcg of fentanyl. To achieve a 1,200 mcg dose, two units of 600 mcg dose were to have been consecutively actuated. Similarly, to achieve a 1,600 mcg dose two units of 800 mcg dose were to have been consecutively actuated.

Open-label dose-titration period: All patients were to have received open-label FSS, in escalating doses from 100 to 1,600 mcg per dose. After each dose, the patient was to have been instructed to record the dosing details and the time and date the dose was taken on the appropriate screen in the electronic diary.

Double-blind, placebo-controlled crossover period: Eligible patients were to have been supplied with a 10-dose study drug pack containing 10 separate blinded unit doses, marked 1 through 10, containing either the “effective” dose (total seven) or matching placebo (total three), randomly allocated in each pack. After each dose, the patient was to have been instructed to record the bottle number and the time and date the dose was taken on the appropriate screen in the electronic diary.

Study Schedule of Events

Table 11: Schedule of Study Events

STUDY EVENT	Screening Visit	Open-label Titration Visit*	Double Blind Visit*	Final Visit/Early Termination Visit*	Follow-up Phone Contact	Unscheduled Visit
Informed Consent	X					
Demographics	X					
Inclusion/Exclusion	X					
Medical History	X					
Cancer History	X					
Prior and Current Therapy & Medication	X					
Detailed Pain Assessment	X					
Physical Examination	X			X		
Oral Cavity Examination	X	X	X	X		
Vital Signs	X	X	X	X		U
12-lead ECG	X			X		
Clinical Laboratory Testing	X		X	X		U
Serum Pregnancy Test	X					
Complete TSQM		X[a]	X			
Issue e-Diary		X	X			
Collect Diary		X	X	X		
Review Diary		X	X	X		U
Issue Study Medications		X	X			U
Provide Training on Use of Study Medications		X	X			U
Collect Unused/Empty Study Medications			X	X		U
Adverse Event Recording	X	X	X	X	X	U
Concomitant Therapy & Medication	X	X	X	X		U

*Daily telephone contact or email contact will be made between the patient and the site to answer any questions and ensure protocol compliance.
TSQM = Treatment Satisfaction Questionnaire for Medication
X = scheduled study event
U = unscheduled, at Investigator's discretion
X[a] = TSQM to be completed before taking the first dose of Fentanyl SL Spray

Source: Protocol number INS-05-001 Appendix 16.1.1 Protocol and Protocol Amendments, page 198/696 of the pdf.

Amendment 4 (04 April 2008): Modifications to Table 11*: Schedule of Events.*

STUDY EVENT	Screening Visit	Open-label Titration Visit*	Double Blind Visit*	Final Visit/Early Termination Visit*	Follow-up Telephone Contact**	Unscheduled Visit
Informed Consent	X					
Demographics	X					
Inclusion/Exclusion	X					
Medical History	X					
Cancer History	X					
Prior and Current Therapy & Medication	X					
Detailed Pain Assessment	X					
Physical Examination	X			X		
Oral Cavity Examination***	X	X	X	X		
Vital Signs***	X	X	X	X		U
12-lead ECG	X			X		
Clinical Laboratory Testing	X		X	X		U
Serum Pregnancy Test	X					
Complete TSQM		X[a]	X[b]	X		
Issue e-Diary		X	X			
Collect Diary			X	X		
Review Diary			X	X		U
Issue Study Medications		X	X			U
Provide Training on Use of Study Medications		X	X			U
Collect Unused/Empty Study Medications			X	X		U
Adverse Event Recording		X	X	X	X	U
Concomitant Therapy & Medication	X	X	X	X		U
Drug Accountability			X	X		

*Daily telephone contact or email contact will be made between the subject and the site to answer any questions and ensure protocol compliance.
**The 30 day follow-up applies to those subjects not rolling over to a separate trial, INS-06-007, an Open-label Multi-center Safety Trial of Fentanyl SL Spray for the Treatment of Breakthrough Cancer Pain.
*** If screening and titration performed on the same day, these procedures do not need to be performed twice.
TSQM = Treatment Satisfaction Questionnaire for Medication;
X = Scheduled study event
U = Unscheduled, at Investigator's discretion
X[a] = TSQM baseline assessment of usual supplemental medication for breakthrough pain on day 1 of Open-label Titration Visit, to be completed before taking the first dose of Fentanyl SL Spray
X[b] = TSQM follow-up assessment of Fentanyl SL Spray medication for breakthrough pain on day 1 of Double-blind Visit

Source: Protocol number INS-05-001 Appendix 16.1.1 Protocol and Protocol Amendments, page 584/696 of the pdf.

Study Conduct

Screening Visit:
All patients were to have signed an informed consent prior to conduct of any study procedures. Key procedures that were to have been conducted at screening included:

- Verification of eligibility on the basis of the inclusion and exclusion criteria
- Medical history
- Medication history
- Physical examination
- Oral cavity examination for abnormalities such as infection, mucositis, cold sores, viral lesions, local irritation, periodontal disease, and tongue piercings
- ECG and laboratory investigations to include hematology, chemistry, urine pregnancy test for females of childbearing potential, and urinalysis (no more than 28 days before the open-label dose-titration period)
- Report number of BTCP episodes and assess persistent cancer related pain intensity in a 24-hour period prior to Screening Visit using the Pain Intensity (PI) 5-point categorical scale (none=0, mild=1, moderate=2, severe=3 and excruciating=4); controlled persistent cancer pain was to have been defined as patients who describe their persistent pain as being moderate (2), mild (1), or none (0) on the 5-point verbal scale.

Patients reporting on average more than 4 breakthrough pain episodes per day, or a persistent cancer pain intensity of greater than moderate intensity were to have been allowed up to 28 days to re-enter the study at the Screening Visit. Patients who were eligible to re-enter the study at the Screening Visit were to have had their 24-hour opioid use adjusted and been on a stable dose for at least seven days prior to the second Screening Visit. A re-screen was to have been allowed once for a given patient.

Patients who qualify for the study by the inclusion and exclusion criteria, report one to four BTCP episodes in the previous 24 hours requiring opioid pain relief medication, and that are on a stable dose of pain relief medication were to have been eligible to enter into the open-label dose-titration period of the study.

Amendment 4 (04 April 2008):

- *The reporting of BTCP episodes was to have been modified to reporting the average number of BTCP episodes per day over the previous 7 days; assessment of persistent cancer related pain intensity was to have remained the same.*
- *The timing of examination and laboratory investigations were to have been modified to physical examinations, oral cavity examinations, laboratory investigations, and ECGs were to have been conducted no more than 35 days before the start of the Open-Label Dose-Titration Period of the study.*

- *All screening procedures were to have been completed for any patient being rescreened.*
- *The Screening Visit and the Open-label Dose-Titration Visit were to have been the same day, with lab results pending.*

Open-label, dose-titration period (up to 21 days):

The open-label dose-titration period was to have defined an effective and tolerable FSS dose to be used in the double-blind, placebo-controlled crossover period of the study. An effective and tolerable dose was to have been a dose of FSS (100, 200, 400, 600, 800, 1200, or 1600 mcg) that can be consistently used to treat two consecutive BTCP episodes.

Patients were to have eligibility verified base on inclusion and exclusion criteria and the following key assessments and procedures:

- Review concomitant medications
- Assess adverse events
- Physical examination, including oral cavity examination
- Issue open-label dose-titration period electronic diary
- Provide open-label dose-titration period study medications
- Complete Treatment Satisfaction Questionnaire for Medication (TSQM) baseline assessment of supplemental analgesia medication for BTCP prior to taking the first dose of FSS

At the start of the open-label dose-titration period, fentanyl naïve patients were to be administered 100 mcg of FSS for the first episode of breakthrough pain. Patients who had experience with, and had tolerated, a stable dose of Actiq or Fentora medications within one-week of study entry were to have initiated FSS dosing according to the following guidelines.

Current Actiq Dose (mcg)	Initial Open-Label Fentanyl SL Spray Dose (mcg)
200	100
400	100
600	200
800	200
1200	400
1600	400

Current FENTORA™ Dose (mcg)	Initial Open-Label Fentanyl SL Spray Dose (mcg)
100	100
200	100
400	200
600	200
800	200

Source: Protocol number INS-05-001 Appendix 16.1.1 Protocol and Protocol Amendments, page 22-23/696 of the pdf.

For patients initiating titration with the 100 mcg dose of FSS, if it was effective and tolerated, the next episode of target BTCP was to be treated with the same dose of

FSS. However, if pain relief was inadequate after 30 minutes then the patient was to have re-dosed with one additional FSS dose. If the pain continued for 30 minutes following the re-dose, patients were to have taken their usual BTCP analgesia ("supplemental medication") as rescue medication. If a patient consistently required an additional 100 mcg of FSS at two subsequent BTCP episodes, the patient was to have been allowed to proceed to the next higher FSS dose strength, 200 mcg. Patients were to have been instructed to wait at least 4 hours before treating another BTCP episode with FSS and not treat more than four episodes of BTCP with FSS per day.

For patients titrating to the 200 mcg dose, if that dose was effective the next episode of target BTCP was to have been treated with the same dose. If pain relief was inadequate after 30 minutes then the patient was to re-dose at 200 mcg. If a patient consistently required additional 200 mcg doses of FSS at two subsequent BTCP episodes, the patient was to proceed to next higher FSS dose strength.

For patients titrating to the 400 mcg dose, if pain relief was inadequate after 30 minutes then the patient was to re-dose with 200 mcg. If a patient consistently required an additional 200 mcg of FSS at the 30 minute point at two subsequent BTCP episodes, the patient was to proceed to next higher FSS dose strength.

The next titration step was to have been the 600 mcg dose. If pain relief was inadequate after 30 minutes then the patient was to re-dose with 200 mcg. If a patient consistently required additional 200 mcg doses of FSS at the 30 minute point at two subsequent BTCP episodes, the patient would have been allowed to proceed to next higher FSS dose strength.

The next higher dose was to have been 800 mcg. If pain relief was inadequate after 30 minutes an additional dose of 400 mcg was to have been permitted. If the patient consistently required additional 400 mcg doses of FSS at the 30 minute point at two subsequent BTCP episodes, the patient would have been allowed to proceed to next higher FSS dose strength.

The next higher dose was 1,200 mcg; two units of 600 mcg dose, consecutively actuated. If pain relief was inadequate after 30 minutes, then the patient was to re-dose with 400 mcg. If the patient consistently required additional 400 mcg doses of FSS at the 30 minute point at two subsequent BTCP episodes, the patient would have been allowed to proceed to next higher FSS dose strength, 1600 mcg delivered as two consecutively actuated 800 mcg units. If the 1600 mcg dose was ineffective the patient was to have been withdrawn from the study.

For each episode of BTCP that was to have been treated with FSS (up to four episodes on any particular day), and there must have been at least four hours between each use of FSS; episodes of target BTCP occurring before four hours were to have been treated

with the patients' usual pain relief medication, patients were to have been instructed to record the following in the diary after each dose:

- Date and onset time of pain
- The "0" time point being immediately prior to FSS administration
- Date, time, and dose of FSS
- Patient's global evaluation of FSS at 30 and 60 minutes post-dose
- Date, time, and strength of FSS re-dosing (if applicable)

The Study Team was to have had daily telephone contact with patients to help manage the diary and respond to study medication questions. The patient, site investigator, and study team were to have assessed the FSS dose titration sequence for each individual patient. The decision to increase, maintain, or decrease the FSS dose was to have been made during the daily telephone assessment with the Investigator who would have assessed the patient's response to the study drug.

A patient who required a significant around-the-clock pain medication adjustment was to have been allowed to re-enter the study at the Screening Period one time. A patient who failed to have determined an effective and tolerable FSS dose or failed to have complied with dosing or evaluation procedures was to have been withdrawn from the study.

In order for patients to be eligible for the double-blind, placebo-controlled crossover period of the study, they would have to have achieved an effective and tolerable FSS dose that can be consistently used to treat two consecutive BTCP episodes.

Amendment 4 (04 April 2008): The duration of the Open-Label, Dose-Titration Period was to have been modified from up to 21 days to up to 26 days.

Double-blind, placebo-controlled crossover period (up to 21 days):

Patients were to have eligibility verified base on inclusion and exclusion criteria and the following key assessments and procedures:

- Review electronic diary from the open-label dose-titration period
- Review concomitant medications
- Assess adverse events
- Oral cavity examination
- Laboratory investigations to include hematology, chemistry, and urinalysis
- Issue double-blind, placebo-controlled crossover diary
- Provide a 10-dose study drug pack
- Training on use of study drug pack
- Collect and inventory all medications used in the open-label dose-titration period
- Complete TSQM follow-up assessment of FSS for BTCP

Patients were to have been supplied with a 10-dose drug pack containing 10 separate unit doses, marked 1 to 10. Patients were to have been instructed to self-administer each dose, according to the correct technique, starting at unit dose 1 and working through to unit dose 10 for each of 10 individual episodes of target BTCP (at least four hours between BTCP episodes and "…not use the Double-blind Period study medication to treat more than two breakthrough pain episodes in a given day."). The blinded doses were to have contained either the "effective" dose found during the open-label dose-titration period (total seven) or placebo (total three), randomly allocated in each pack.

If pain relief was inadequate after 30 minutes following a FSS dose, patients were to have been permitted to take their usual breakthrough pain medication as rescue.

For each episode of target BTCP that was to have been treated with blinded study medication, patients were to have been instructed to record the following in the diary after each dose:

- Date and onset time of pain
- The "0" time point being immediately prior to FSS administration
- Date and time of study medication
- Date and time of rescue medication
- Pain intensity using a horizontal visual analog scale (VAS), where one anchor represented "no pain" and the other anchor represented "the worst possible pain"
- Pain intensity at 0, 5, 10, 15, 30, 45 and 60 minutes after the onset of a BTCP episode
- Pain relief using a 5-point categorical scale (i.e., 0: no relief, 1: a little relief, 2: moderate relief, 3: a lot of relief, 4: complete relief)
- Pain relief at 5, 10, 15, 30, 45 and 60 minutes after the onset of a BTCP episode
- Patient's Global Evaluation of Study Medication using a 5-point categorical scale (i.e., 0: poor, 1: fair, 2: good, 3: very good, and 4: excellent) at 30 and 60 minutes

The Study Team was to have daily telephone contact with the patients to manage their electronic diaries and respond to study medication questions. The double-blind phase was to have been completed when the 10 doses in the drug pack have been used, or more than 21 days have elapsed. The Investigator was to have the option to conduct unscheduled visits during the double-blind, placebo-controlled crossover period in order to include additional assessments as needed.

Amendment 4 (04 April 2008): The duration of the Double-Blind, Placebo-Controlled Crossover Period was to have been modified from up to 21 days to up to 26 days.

End-of-Treatment ("Final Visit/Early Termination Visit"):

At the end of the double-blind, placebo-controlled crossover period (i.e., completed the 10 double-blind treatments in the drug pack or more than 21 days have elapsed), patients were to have returned for final assessments. Patients who discontinued early were also to have returned for a final assessment. The following assessments and procedures were to have been performed:

- Review electronic diary from the double-blind, placebo-controlled crossover Period
- Review intervening history and concomitant medications
- Assess adverse events
- Physical examination, including oral cavity examination
- ECG and laboratory investigations to include hematology, chemistry and urinalysis
- Collect and inventory all study medications used in the double-blind, placebo-controlled crossover period
- Complete TSQM

Amendment 4 (04 April 2008): The duration of the Open-Label, Dose-Titration Period and the Double-Blind, Placebo-Controlled Crossover Period were to have been modified from up to 21 days to up to 26 days, and the maximum study duration for individual patients was to have been modified from 42 days to 52 days accordingly.

Follow-up

The Study Team was to have made telephone contact with patients 30 days following the End-of-Treatment ("Final Visit/Early Termination Visit") to perform a safety assessment. The safety assessment was to have included asking the patient the following questions:

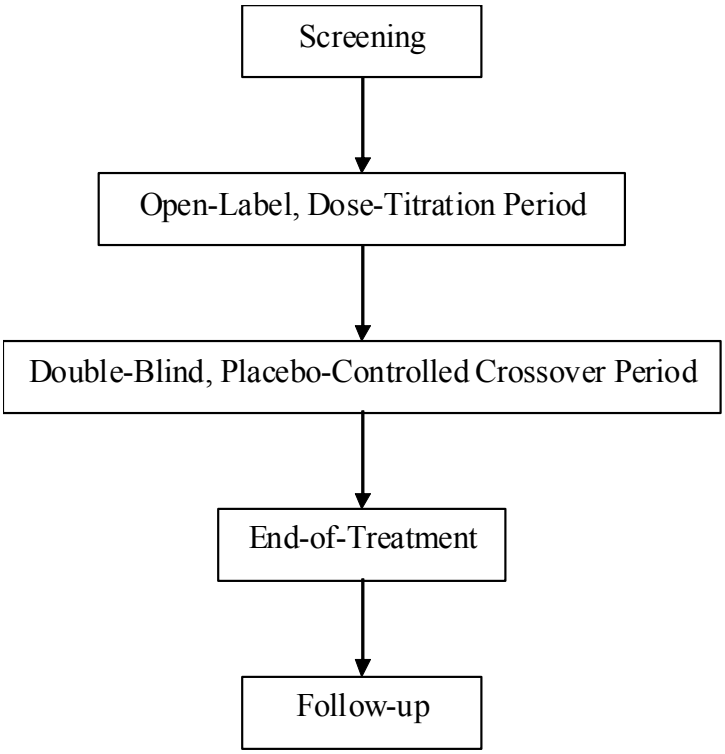
- "Have you had any medical problems since your last visit?"
- "Have any medical problems present at your last visit changed, i.e., stopped, worsened, or improved?"
- "Have you taken any new medicines, or changed your current medication regimen since your last visit?"

Amendment 3 (06 December 2007): The telephone contact at 30 days following the End-of-Treatment ("Final Visit/Early Termination Visit") was not to have been required for patients entering the Open-label Multi-center Safety Trial of Fentanyl SL Spray for the treatment of breakthrough cancer pain (i.e., study INS-06-007).

Amendment 4 (04 April 2008): The telephone contact following the End-of-Treatment ("Final Visit/Early Termination Visit") was to have been modified from 30 days to 28 to 35 days following the End-of-Treatment ("Final Visit/Early Termination Visit") for patients not entering the Open-label Multi-center Safety Trial of Fentanyl SL Spray for the treatment of breakthrough cancer pain (i.e., study INS-06-007).

Study Flow Chart

Figure 8: Study flow chart



Removal of Subjects from Therapy or Assessment

Each patient was to have been free to withdraw from the trial at any time without prejudice to further treatment. A patient who withdrew prior to receiving the study medication was not to have been considered a dropout and was not to have been included in the database. Patients were to have been discontinued from the trial for any of the following reasons, if deemed appropriate, by the Investigator or the Applicant:

- Unable to define an effective and tolerable FSS dose during the open-label dose-titration period
- Intercurrent illness, adverse events, or surgery as determined by the Investigator if not specified in the protocol
- Serious adverse events or adverse events that contraindicate further study drug administration
- Signs or symptoms suggesting toxicity
- Protocol violation
- Not in the patient's best interest to continue in the trial

- Applicant's decision to terminate the study or study site
- Regulatory agency decision to terminate the study or the study site

If a patient discontinued from the trial for any reason the Investigator was to have made every effort to perform the same follow-up safety assessments, laboratory tests, and medical examinations scheduled for patients who completed the trial (i.e., "Final Visit") within two days of the last study medication dose. If a patient was discontinued from the trial, the time, date and reason for early discontinuation was to have been noted in the source documents and appropriate CRFs. All patients were to have been contacted by telephone approximately 30 days after the last dose of study medication.

In the event that a patient was discontinued early from the trial because of an adverse event or serious adverse event, the procedures regarding safely reporting were to have been followed.

Concurrent therapy

Medications or therapies for a chronic disease condition and medications to help manage pain (e.g., bisphosphonates, steroids, Neurontin) were to have been allowed throughout the study provided the medication or therapy was stable in dose and frequency for at least one week prior to the Screening Visit.

Agonist-antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol) were to have been prohibited.

Short-acting commercially available fentanyl medications used to help manage breakthrough pain (e.g., Fentora and Actiq) were to have been allowed up to one-week prior to study entry onto the open-label dose-titration period, but were to have been prohibited during the open-label dose-titration period and the double-blind, placebo-controlled crossover period of the study.

Other medications considered necessary for the patient's welfare and that would not impair or alter a patient's ability to dose study medication and record pain and medication evaluations, were to have been allowed at the discretion of the Investigator.

An accurate record of all concomitant medications and therapies including the medication or therapy name, the reason for its use, dose, frequency, and start and stop dates was to have been documented in source documents and the CRF.

Rescue Medication

Patients were to have been allowed their usual BTCP analgesia ("supplemental medication") as rescue 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, patients were to have recorded the dose of study medication used in their electronic diary. Response information was to have been recorded using the pain scales prior to and following study drug use.

The following measurements were to have been recorded for the evaluation of efficacy:

1. Pain intensity (PI): Patients were to have rated their pain intensity using a horizontal visual analog scale ranging from “no pain” to “the worse possible pain.” PI was to have been recorded immediately before FSS dosing (time 0) and at 5, 10, 15, 30, 45, and 60 minutes after dosing.
2. Pain relief (PR): Patients were to have scored their pain relief using a 5-point categorical scale (0: no relief, 1: a little relief, 2: moderate relief, 3: a lot of relief, 4: complete relief). Pain relief was to have been recorded at 5, 10, 15, 30, 45, and 60 minutes of the BTCP episode onset.
3. Global assessment: The Patient’s Global Evaluation of Study Medication was to have been recorded as a summary score that took into account of the overall impression of treatment effect using a 5-point categorical scale (0: poor, 1: fair, 2: good, 3: very good, and 4: excellent) at 30 and 60 minutes after study drug administration for each BTCP episode.
4. Treatment Satisfaction Questionnaire for Medication (TSQM): At baseline, patients were to have been instructed to base their responses on only the use of their usual rescue (“supplemental”) medication for BTCP. At the subsequent visits in which patients were to have completed the questionnaire and had been taking the FSS, patients were to have been instructed to base their responses on only their use of the FSS for BTCP.
5. Rescue (“supplemental”) medication: Time to rescue medication and the amount of rescue medication used for each treatment episode was to have been recorded.

The derived variables in this trial were to have included:

1. Pain Intensity Difference (PID): PIDs were to have been defined as the numerical differences in pain intensity at the various time points versus baseline (time 0).
2. Summed Pain Intensity Differences (SPID): The PIDs were to have been cumulatively summed across time, creating SPID.
3. Total Pain Relief (TOTPAR): The pain relief scores were to have been cumulatively summed across time, creating the TOTPAR summary score.

4. Rescue ("supplemental") medication: The derived variables for this were to have been median time to rescue medication, percent of episodes requiring rescue medication, and average amount of rescue medication taken.

Primary Efficacy Endpoint

The primary outcome variable was to have been the sum of pain intensity differences at 30 minutes (SPID30) after dosing for FSS versus placebo during the double-blind, placebo-controlled crossover period of the Study.

Secondary Efficacy Endpoints

The secondary efficacy endpoints were to have been TOTPAR at 30 minutes (T0TPAR30), Patient's Global Evaluation of Study Medication at 30 minutes, and PID at time points up to 30 minutes.

Amendment 4 (04 April 2008): The secondary efficacy endpoint of PID at time points up to 30 minutes was to have been deleted such that the secondary efficacy endpoints are TOTPAR30 and Patient's Global Evaluation of Study Medication recorded at 30 minutes.

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

Beginning with the first dose of study medication and throughout the study, adverse events 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 to have been responsible for assessing the relationship of adverse events to the study medication; relationship was to have been classified as not related, unlikely related, probably related, or possibly related (see Protocol INS-05-001 Section 8.12.3 page 39/696 of pdf for definitions). All adverse events were to have been followed until they were resolved, stabilized, or until all attempts to determine event resolution were to have been exhausted. 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.

Adverse events were to be coded using a standardized dictionary (Medical Dictionary for Regulatory Activities [MedDRA] Version 10.1). Incidence of adverse event analyses was to be presented overall, by system organ class and preferred term. Severity and relationship to study medication of the incidence of adverse events were also to be presented. Adverse events causing early withdrawal and incidence of SAEs were to be summarized. Treatment-emergent adverse events (TEAEs) were to be recorded through the last study visit; event outcome at resolution or time of last follow-up was to have been recorded as event resolved, resolved with sequelae, ongoing, or death.

Statistical Analysis

Three datasets were to have been used for analysis: Safety, intent-to-treat, and per-protocol. The definitions of these datasets follow:

- Safety Population: All randomized patients who received at least one dose of study medication.
- Intent-to-Treat (ITT) Population: All randomized patients who had at least one pain measurement following administration of study drug.
- Per-protocol (PP) Population: The PP dataset was to have contained patients in the ITT population and had no protocol violation such that it might have effected efficacy measurements. All decisions to exclude patients/assessments were to have been determined by the Applicant prior to unblinding the data.

Primary efficacy analysis

The primary outcome variable was to have been the SPID30 after dosing for FSS versus placebo during the double-blind, placebo-controlled crossover period of the trial.

- All efficacy analyses were to have been carried out using the ITT population. Some endpoints may also have been analyzed using the PP population.
- PI, PID, and SPID were to have been analyzed using a single mixed model in which PI was the dependent variable. Inference on PID and SPID at all time points, including the primary SPID30, was to have been done within this model, because these measures are linear combinations of PI at various time points. The model's fixed effects were to have been treatment, time, and treatment-time interaction. The random effects were to have been patient and BTCP episode within patient.
- An analogous approach was to have been used for the analysis of PR and TOTPAR, with PR treated as a continuous dependent variable.
- Within a BTCP episode treated with study medication, pain measures PI, PID, SPID, PR, and TOTPAR obtained after the use of rescue ("supplemental") medication were to have been treated as missing in the primary analyses for the various time points. A sensitivity analysis of analgesic efficacy was to have been performed by replacing pain measures obtained after the use of rescue ("supplemental") medication by the baseline PI (baseline observation carried

forward, BOCF. For the analysis of PR the 5 minute value will be carried forward.) Then the resulting data was to have been summarized within each patient as the difference of the averages over the available BTCP episodes treated with FSS and with the placebo study medication. These within-patient differences were to have been analyzed with the Wilcoxon signed rank test. A full description of the treatment of missing data for other reasons and imputation was to have been addressed in the Statistical Analysis Plan (SAP), which was to have been completed before unblinding.

- The Global Evaluation of Study Medication was to have been analyzed using an analysis of variance (ANOVA) with fixed effect of treatment and random effects for patient and episode.
- Patient satisfaction with treatment medication was to have been assessed among all enrolled patients at baseline and at the end of titration period by the TSQM. The Effectiveness, Side Effects, Convenience and Overall Satisfaction domains of medication experiences derived from the TSQM, as well as the individual questionnaire items, were to have been summarized at baseline and at Visit 1 of the double-blind, placebo-controlled crossover period and as change from baseline to the Visit 1 of the double-blind, placebo-controlled crossover period. Because the assessments were to have been completed before randomization, only descriptive statistics were planned to be presented.
- Incidence of use of rescue ("supplemental") medication in a pain episode was to have been compared between treatments using a repeated measures generalized estimating equation (GEE) model. Time to rescue ("supplemental") medication within each episode was to have been compared between treatments using the Cox Proportional Hazards model, accounting for multiple episodes within patients. Descriptive statistics for incidence of and time to rescue ("supplemental") medication use were to have been specified in the SAP.
- Exploratory modeling and subgroup analyses was to have been performed using factors of interest such as age, gender, type of around-the-clock pain medication, and optimal dose of FSS. Additional sensitivity analyses may have been specified in the SAP.

Amendment 4 (04 April 2008):

- *The following was to have been <u>added</u>: "The primary analysis of SPID30 is as follows: Within each subject SPID30 will be summarized over breakthrough pain episodes treated with Fentanyl SL and over episodes treated with placebo. Within a subject and treatment combination, if a given time point has a missing value for some episodes and an actual value for other episodes, the average from the available episodes will be used. If a given time point has missing values at all episodes then the most recently available average will be used. Next, the difference within subject of the two SPID30 summaries will be calculated. Additionally within each subject the average baseline pain intensity will be calculated over all breakthrough pain episodes treated with study medication (regardless of treatment). Finally an analysis of covariance of the within-subject*

SPID30 differences will be performed, with the within-subject average baseline pain intensity as covariate. The secondary endpoints TOTPAR30 and Subject's Global Evaluation of Study Medication recorded at 30 minutes will be analyzed similarly.

The overall type 1 error for the primary and secondary analyses will be 0.05. The p-values from the two secondary endpoints will be adjusted for multiple comparisons using Hochberg'smethod, but neither endpoint will be considered statistically significant unless the primary endpoint has been declared significant.

Sensitivity analyses will be performed by analyzing within-subject treatment differences in SPID30, TOTPAR30 and Subject's Global Evaluation of Study Medication with the Wilcoxon signed rank test."

- *The following was to have been deleted: "A sensitivity analysis of analgesic efficacy will be performed by replacing pain measures obtained after the use of supplemental medication by the baseline PI (baseline observation carried forward, BOCF. For the analysis of PR the 5 minute value will be carried forward.) Then the resulting data will be summarized within each subject as the difference of the averages over the available breakthrough pain episodes treated with Fentanyl SL Spray and with the placebo study medication. These within-subject differences will be analyzed with the Wilcoxon signed rank test."*

Safety analysis

The primary safety assessments, percent of patients withdrawn due to AEs, percent of patients with SAEs, and percent of patients with clinically meaningful changes in laboratory parameters, were to have been summarized descriptively. No statistical comparisons were planned.

Additional analyses were to have included displays of the number and percentage of patients reporting at least one AE (incidence table), total number of episodes of each AE by body system and by severity, and total number of episodes of each AE by body system and by attribution.

For each laboratory parameter, descriptive statistics (n, mean, standard deviation, median and range) was to have been tabulated for baseline and final values, and change from baseline for patients who have both baseline and final values. A scatter diagram depicting baseline and final values for each patient was to have been presented along with a shift table of changes from baseline based on clinically relevantly normal, high or low values. Clinically relevant limits for the laboratory parameters were to have been specified in the SAP.

Interim analysis: There was no planned interim analysis.

Final Statistical Analysis Plan (SAP): A final SAP was to have been signed off by the Applicant prior to unblinding. The SAP was to have provided detailed description of all intended analyses, including the treatment of missing data and criteria for the PP analysis cohort. The SAP was to have also indicated any changes in statistical methods from this protocol.

Protocol Amendments

The Applicant submitted five amendments to the NDA (see Table 10). Three of the amendments were implemented prior to the first patient enrollment. This protocol review reflected the original protocol with incorporation of the first three amendments. Protocol amendments implemented after the first patient enrollment are indicated at the end of the respective protocol sections in *italics*.

Protocol amendment 3 and 4 were implemented 2 months and 7 months after the first patient enrollment, respectively. However, the substance of the amendments did not appear to substantively impact the overall trial design or outcome.

Results

Neither the protocol trial nor the results of the trial contained information on how patients were instructed to use the FSS and whether there was supervision or observation period following the first FSS dose. An information request was sent to the Applicant in this regard. The Applicant responded:

- "At the time of entry into the protocol, patients were trained on the use of Fentanyl Sublingual Spray with the Patient Instructions for Spray Device… and were given take-home instructions… illustrating the proper use of Fentanyl Sublingual Spray… Sites were also provided with empty "dummy" spray devices (devices did not contain any liquid) with which the sites could use to demonstrate the proper use of the devices while patients were in the office."
- "Per protocol… daily telephone contact or email contact was made between the site and the subject to answer any questions and ensure protocol compliance and understanding."

It appears patients were trained to use the FSS device in an office setting, but there was not a direct supervision or observation period with the actual first use of FSS.

6.1.2 Demographics

Table 12 below presents a summary of subject demographics for the open-label, dose-titration and double-blind placebo-controlled crossover periods.

Table 12: Summary of patient demographics

Characteristic	Titration N=130	Double-blind (ITT) N=96
Age (yrs)		
Mean (SD)	55.6 (12.2)	54.1 (11.7)
Median	55.8	54.6
Min, Max	24, 85	24, 85
< 65	100 (76.9%)	80 (83.3)
≥ 65	30 (23.1%)	16 (16.7)
Gender, n (%)		
Male	61 (46.9)	44 (45.8)
Female	69 (53.1)	52 (54.2)
Race*, n (%)		
Caucasian	118 (90.8)	87 (90.6)
Black	9 (6.9)	7 (7.3)
Pacific Islander	1 (0.8)	1 (1.0)
Native American	1 (0.8)	1 (1.0)
Other	2 (1.5)	1 (1.0)

* Patient may be counted under multiple categories
Source: INS-05-001 body FINAL STUDY REPORT, page 137-138/397 of the pdf

Of the 130 patients in the open-label, dose-titration population, 61 (46.9%) were men, the median age was 55.8 years (range, 24 to 85 years), the majority of patients (76.9%) were younger than 65 years and they were Caucasian (90.8%). There were no important differences in the demographic characteristics between the open-label, dose-titration and double-blind placebo-controlled crossover periods of study.

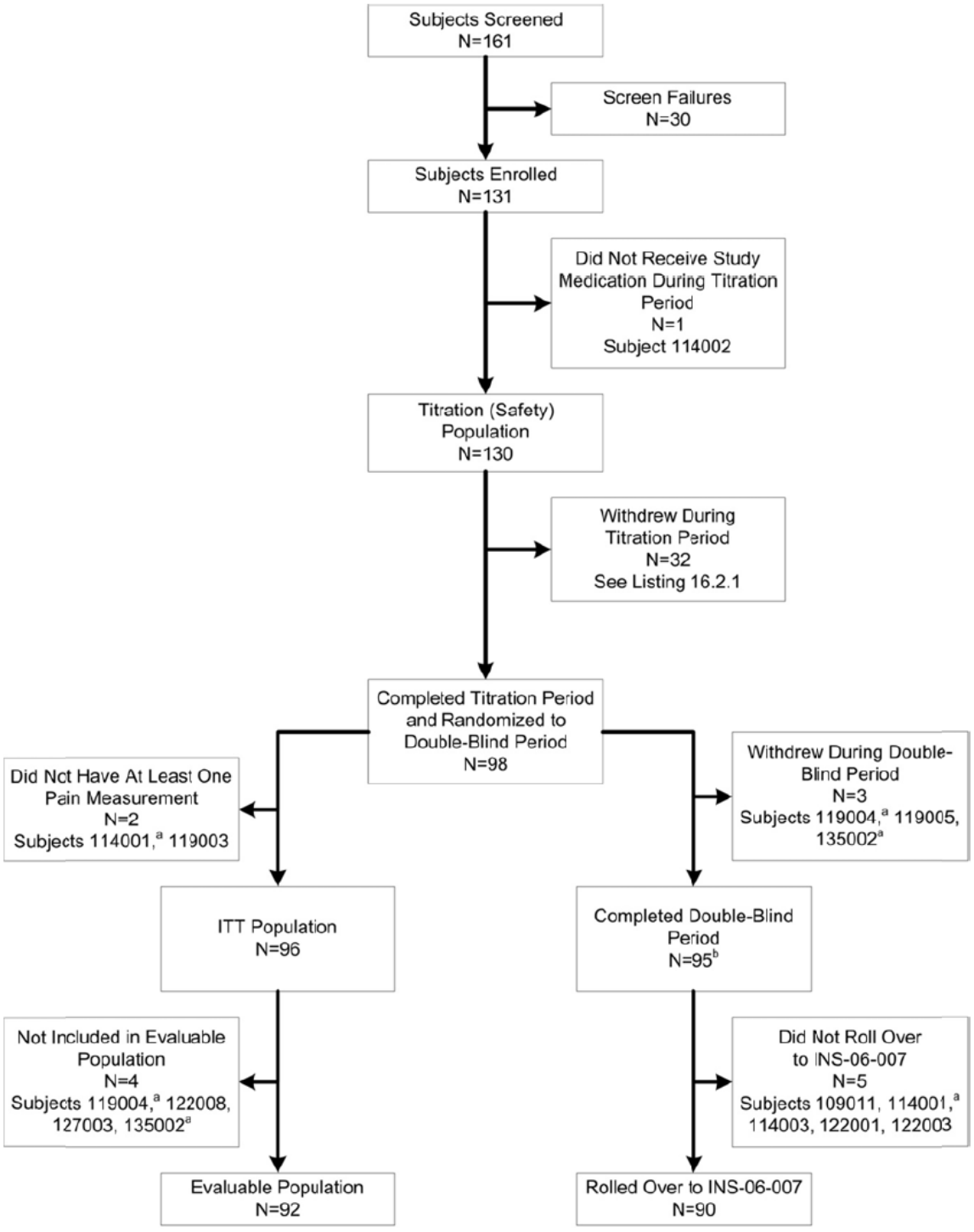
The most frequently used concomitant medications were fentanyl (40.1%), oxycodone (27.7%), hydromorphone hydrochloride (25%), and morphine sulfate (25%). The most commonly used (≥15%) rescue medications for BTCP were hydromorphone hydrochloride (23%), oxycodone (22%), hydrocodone/acetaminophen (22%), and oxycodone (16%). There were no differences in the supplemental BTCP medication used in the open-label, dose-titration and double-blind placebo-controlled crossover periods of study.

6.1.3 Subject Disposition

The details of the patient disposition in this trial appeared unclear and were difficult to follow. Information requests were sent to the Applicant asking for a patient disposition flow diagram to account for all patients in each study period (i.e., screening, titration, randomization, intention-to-treat (ITT) population, and patients who completed the entire study) and all patients that withdrew from each study period. The Applicant provided the requested information. The Applicant acknowledged that 161 patients were screened for this trial rather than the 160 patients in Table 1: Disposition Flow Diagram for INS-05-001 of 1.11.3 Efficacy Information Amendment. A corrected Table 1: Disposition Flow

Diagram for INS-05-001 was provided. Figure 9 below illustrates patient disposition in study INS-05-001.

Figure 9: Patient disposition



a. Subjects 114001, 119004, and 135002 each appear twice in this diagram.
b. Subjects 114001 and 119003 were excluded from the ITT Population, but are included within the group that completed the double-blind period. However, these two subjects have no efficacy data due to an equipment malfunction.

Source: SN0005 1.11.3 Efficacy Information Amendment, page 5/8 of the pdf

All the patients in the trial were enrolled across 43 sites within the United States. A total of 161 patients were screened and 131 patients (81%) were enrolled for participation in the trial. Of the 131 enrolled patients, 130 (99.2%) entered the open-label, dose-titration period, and 130 (100%) received at least one dose of FSS and were included in the Safety Population. One patient, ID number 114002, met all inclusion criteria and formally entered the open-label, dose-titration period but did not receiving any study drug.

A total of 32 of 130 patients (24.6%) discontinued during the open-label, dose-titration period, leaving 98 patients continuing on to the double-blind, placebo-controlled cross over period. There were a total of three patients (3.1%) who discontinued during the double-blind placebo-controlled crossover period. The reasons for early discontinuation from the trial during the open-label dose-titration and double-blind placebo-controlled crossover periods are as indicated in Table 13. The “Total” was the sum of patients from the open-label, dose-titration and the double-blind placebo-controlled cross over periods. Therefore, the number of patients who discontinued early from the open-label, dose titration period was the difference between the “Total” and the “Double-Blind” columns. For example, the total number of patients who discontinued from the open-label, dose-titration period was 32 (i.e., 35 (“Total”) minus 3 (“Double-Blind”).

Table 13: Reason for discontinuation

Site:Overall	Total (N=130)	Double-Blind (N=98)
Treated During Titration Period (Titration Population, Safety Population)	130 (100.0%)	
Randomized to Double-Blind	98 (75.4%)	98 (100.0%)
Double-Blind Treatment/Post-Treatment Pain Assessment (ITT Population)	96 (73.8%)	96 (98.0%)
Completed Double-Blind	95 (73.1%)	95 (96.9%)
Early Terminated From Study	35 (26.9%)	3 (3.1%)
UNABLE TO DETERMINE A SUCCESSFUL DOSE DURING THE TITRATION PERIOD	3 (2.3%)	0 (0.0%)
INTERCURRENT ILLNESS, AE OR SURGERY	1 (0.8%)	0 (0.0%)
AES AND SAES THAT CONTRAINDICATE FURTHER ADMINISTRATION OF THE STUDY DRUG	7 (5.4%)	1 (1.0%)
FAILURE TO COMPLY WITH ADMINISTRATIVE REQUIREMENTS OF THE PROTOCOL	2 (1.5%)	1 (1.0%)
SIGNIFICANT PROTOCOL VIOLATION	1 (0.8%)	0 (0.0%)
INVESTIGATOR DECISION	2 (1.5%)	0 (0.0%)
SUBJECT DECISION FOR WITHDRAWAL	16 (12.3%)	1 (1.0%)
OTHER*	3 (2.3%)	0 (0.0%)
Completed 10 Doses According to Protocol	79 (60.8%)	79 (80.6%)
Roll-over to Safety Portion of Study	90 (69.2%)	90 (91.8%)

* Subject 102002 discontinued due to: SUBJECT NO LONGER FIT CRITERIA DUE TO PAIN INJECTIONS.
Subject 108001 discontinued due to: PT NONCOMPLIANCE.
Subject 137006 discontinued due to: SUBJECT NO LONGER HAVING BREAKTHROUGH PAIN.

Source: INS-05-001 body FINAL STUDY REPORT, page 110/397 of the pdf

The two most common reasons for discontinuation from the open-label, dose-titration period were patients decided to withdraw and AEs/SAE. The category of patient's decision to withdraw from the trial was non-descriptive and uninformative, and required a better understanding of actual reason(s) that lead to patient discontinuation from the trial. There were a total of 16 patients (15 during the open-label, dose-titration period and one during the double-blind, placebo-controlled crossover period) in this category. A review of the source material showed patients who discontinued from the trial because of "patient decision" included adverse event (patient 111002), "patient felt overmedicated and also had mouth sores" (patient 140002), and "concern of A/E" (patient 101001). Further review of the case report forms of the remaining 13 patients in the "patient decision" category showed patients decided to discontinue from the trial for a variety of reasons, which included disliked use of electronic-diary, unable to follow titration procedures, preference for their rescue medication over FSS, difficulty in attending appointments, disliked taste of medication, and decision to pursue intrathecal morphine pump.

The two patients who were discontinued because of "investigator decision" during the open-label, dose-titration period were for reasons of "unable to determine a successful dose during the titration period" (patient 138002) and "undesirable side effects" (patient 142002). One patient (105003) was discontinued because of "intercurrent illness, AE or surgery." An information request was sent to the Applicant asking for clarification on "concern of A/E" and "intercurrent illness, AE or surgery." The Applicant responded:

- "Patient [101001] withdrew from study over concern for AE... Reason for withdrawal is confirmed, occurrence of a fistula not related to patients study participation." Based on the response to our information request and the patient narratives in the final study report, patient 105003 had metastatic lung cancer to the spine that required spinal surgery and patient was discontinued from the trial during the open-label dose-titration period because of his overall poor prognosis.

The Applicant confirmed that patient 101001 decided to discontinue from the trial because of personal concerns for AEs, and not because of occurrence of AEs. The explanation for discontinuing patient 105003 early from the trial appeared to be consistent with cancer-related intercurrent illness.

Table 13 indicated three (2.3%) patients were "unable to determine a successful dose during the open-label, dose-titration period." However, Table 14.3.1 Summary of Successful Titration Dose Level Overall and by Site (Titration Period) indicated 32 (24.6%) patients "Did not Attain Successful Dose level." An information request was sent to the Applicant for this apparent discrepancy. The Applicant responded:

- "The accurate number of subjects who were unable to determine a successful dose during titration period is n=3 (see INS-05-001 CSR Table 10-1). For the purposes of Table 14.3.1, the assumption was used that if subjects did not complete the titration period, they did not attain a successful dose. Therefore, when Table 14.3.1 shows that the n=32 did not attain successful dose, it is

actually the n=32 did not enter the double-blind period. The n=32 is a compilation of all of the subjects who did not enter the double-blind period."

The Applicant confirmed there were only three patients who did not achieve a successful dose during the open-label, dose-titration period and they did not proceed onto the double-blind, placebo-controlled cross over period. Based on the Applicant's response, for Table 14.3.1 their assumption that the 32 patients who did not complete the titration period because they did not attain a successful dose was in error. The 32 patients were actually the total number of patients who discontinued from the open-label, dose-titration period of the trial.

There were a total of three patients who discontinued early for "Other" reasons during the open-label, dose-titration period; patient 102002 required parenteral pain relief medication, patient 137006 no longer had BTCP, and patient 108001 was non-compliant. An information request was sent to the Applicant for clarification of the apparent internal discrepancy that patient 108001 discontinued from the trial for "Other" reasons and for being non-compliant. The Applicant responded:

- "…did not comply with drug dosing instructions and did not enter data in the electronic diary… the investigator's judgment, the Other category was more appropriate…."

The Applicant's response suggested the situation with patient 108001 was a compliance issue, and this patient should have been categorized as non-compliant rather than "Other."

There was one patient (110003) with a protocol violation during the open-label, dose-titration period that lead to discontinuation from the trial; see Protocol violation and deviations for details.

There were 98 (75.4%) patients who completed the open-label dose-titration period by achieving an effective and tolerable FSS dose. All of these patients entered the double-blind placebo-controlled crossover period and received a 10-dose pack containing 10 separate "blinded" unit doses, marked 1 through 10, containing either the titrated FSS strength (total seven) or placebo (total three), in a random order. Patients were to self-administer each dose, according to the correct technique, starting at unit dose 1 and working through to unit dose 10 for each of 10 individual episodes of target BTCP (at least 4 hours between BTCP episodes and "…not use the Double-blind Period study medication to treat more than two breakthrough pain episodes in a given day.")*. If pain relief was inadequate after 30 minutes following a FSS dose, patients were to take their usual breakthrough pain medication as rescue. Of the 98 patients enrolled in the double-blind placebo-controlled crossover period, there were a total of three patients (3.1%) who discontinued during this period. The reasons for discontinuation were AEs/SAE (patient 119005), failure to comply with administrative requirements (patient 119004), and patient decision (patient 135002). Review of the narrative for patient 119005 showed the patient was hospitalized for progression of the underlying cervical cancer, was admitted to hospice care, and died. It would seem this patient should have

been categorized as “intercurrent illness, AE or surgery” rather than AEs/SAE. The reason for patient 135002’s decision to discontinue from the trial was “doesn’t need drug anymore.” A total of 95 (96.9%) patients completed this part of the trial, but not all treated 10 episodes. There were 79 (80.6%) patients who completed 10 doses according to protocol.

* In the INS-05-001 Final Study Report page 29/397 of the pdf indicated “New episodes of breakthrough pain were to be treated with study medication after > 2 hours had elapsed from the last episode treated with study medication.” and page 42/397 of the pdf indicated “Once a breakthrough pain episode was treated with Fentanyl SL Spray, the subject was to wait for at least 4 hours after the last dose of Fentanyl SL Spray before treating another episode.” An information request was sent to the Applicant for this apparent internal discrepancy. The Applicant responded:

- “There is a typographical error in the CSR (2 hours should read as 4 hours on page 29/357 of submission). During the study, new episodes of breakthrough pain were to be treated with study medication after ≥ 4 hours had elapsed from the last episode treated with study medication.”

Based on review of the source material and the Applicant’s responses to our information requests, Table 14 was generated to more accurately reflect the reasons for early patient discontinuation from the trial.

Table 14: Reason for discontinuation (revised)

Reason	Open-label Period n (%)*	Double-blind Period n (%)**
Patient decision	13 (10.0)	1 (1.0)
AEs/SAE	9 (6.9)	0 (0)
Unable to determine successful dose	4 (3.1)	0 (0)
Other	2 (1.5)	0 (0)
Non-compliant	2 (1.5)	1 (1.0)
Intercurrent illness, AE or surgery	1 (0.8)	1 (1.0)
Protocol violation	1 (0.8)	0 (0)
Total	32 (24.6)	3 (3.1)

*The number of patients (n) and percent (%) of patients was based on N=130 patients during this period
**The number of patients (n) and percent (%) of patients was based on N=98 patients during this period

The ITT population was defined as all patients in the randomized double-blind placebo-controlled crossover period who took at least one dose of study medication and had at least one pain measurement following administration of study medication. Of the 98 randomized patients in the double-blind placebo-controlled crossover period, 2 patients (114001 and 119003) did not have at least one pain measurement and were excluded

from the ITT population. This left 96 (98.0%) patients in the ITT population as summarized by dose group in Table 15 below. A per-protocol population was not defined or analyzed.

Table 15: Summary of randomized patients by FSS dose group

Summary of Successful Titration Dose Level Overall and by Site (Double-Blind Period)
ITT Population (N = 96)

Site: Overall	Total (N=96)
Dose n(%)	
100 mcg	4 (4.2%)
200 mcg	7 (7.3%)
400 mcg	14 (14.6%)
600 mcg	15 (15.6%)
800 mcg	23 (24.0%)
1200 mcg	20 (20.8%)
1600 mcg	13 (13.5%)

Source: INS-05-001 body FINAL STUDY REPORT, page 235/397 of the pdf

According to the Applicant's submission (Table 13) there were a total of seven patients who discontinued from the trial due to AEs: six patients (4.6%) during the open-label, dose-titration period and one patient (1.0 %) during the double-blind, placebo-controlled crossover period. However, after reviewing the Applicant's source material and responses to our information requests, the total number of patients who discontinued from the trial due to AEs has been adjudicated to be nine (6.9%) and all these patients discontinued from the trial during the open-label, dose-titration period (Table 14).

Protocol violations and deviations

The Applicant referred to protocol "violations" and "deviations." An information request was sent to the Applicant asking for their distinction between protocol "violation" and "deviation." The Applicant responded:

- "For purposes of this protocol, a protocol deviation is defined as unapproved, unanticipated or anticipated departure from the protocol once a subject is enrolled… The term "protocol violation" was used in the CSR and statistical tables as a synonym for "protocol deviation." There is no separate definition for protocol violation."

Listing II.F Protocol Violations/Deviations Titration Population (N=130) indicated there were a total of 94 patients who violated/deviated protocol. One of these patients (0.8%) was discontinued from the trial because of protocol violations/deviations, which occurred during the open-label dose-titration period. This patient (110003) entered into the study without a definite diagnosis of cancer, and was found to be deceitful with respect to cancer diagnosis, and in fact did not have cancer.

The number of patients who discontinued from the double-blind period because of protocol violations/deviations was unclear. An information request was sent to asking for the location of protocol violation/deviation for patients in the double-blind period, and we were referred to Listing II.F in 1.11.3.1 Response to Division of Scientific Investigation Comments. However, this listing indicates "Protocol Violations/Deviations Titration Population (N=130)." A second information request was sent to the Applicant asking for the location of the protocol violation/deviation for patients in the double-blind period and the Applicant was asked to confirm there were no early patient withdrawals from the trial during this period. The Applicant responded:

- The Applicant submitted Listing 16.2.28, which lists patients with protocol violations/deviations during the double-blind period.
- "Three subjects terminated early from the Double-Blind Period (subjects 135-002, 119-004, 119-005)… Of these three subjects, only subject 119-005 had a protocol deviation during the Double-Blind Period; however, this subject's protocol deviation was not the reason for termination."

This information indicates there were 45 patients who had protocol violation/deviation during the double-blind period and there were 3 patients who were discontinued early from the trial during the double-blind period. However, none of the patients who were discontinued early from the trial during the double-blind period was for reason of protocol violations/deviations.

Of note, the Applicant indicated there were 45 patients who had protocol violations/deviations during the double-blind period (Listing 16.2.28). However, only 42 of these patients were accounted for in Listing II.F in 1.11.3.1 Response to Division of Scientific Investigation Comments. Apparently, the 3 patients (127001, 127002, and 127003) from site 127 were missing from Listing II.F. This would mean there were a total of 97 (not 94) patients who violated/deviated protocol during this trial. This apparent internal discrepancy is unlikely to confound the trial results because there was only one patient that was discontinued early from the trial because of protocol violations/deviations, and this patient was accounted for in the open-label dose-titration period.

The Applicant indicated "Protocol violations and deviations were identified and listed by subject. The numbers of subjects were summarized for each category specified below:" However, this data set was not included with the submission and an information request was sent asking for the location of this data set. The Applicant responded:

- "Through an oversight during the original final study report development and filing of the NDA, the dataset requested was inadvertently left out of the application…."

The Applicant provided Table 14.1.11: Summary of protocol deviations/violations, Listing 16.2.27: Protocol violations/deviations during open-label dose-titration period, and Listing 16.2.28: Protocol violations/deviations during double-blind placebo-controlled crossover period. However, the violations/deviations categories in each Listing were incomplete. An information request was sent asking for "…Why are there patients listed with deviations without categorizations? Ex. Patient 105004 missed e-

diary evaluations, and did not wait an appropriate length of time between pain episodes before treating another episode. Pt 105005 missed a diary assessment and dosed in error." The Applicant responded:

- The protocol deviation numbering scheme was developed as a way to categorize deviations during the conduct of the study. Site Investigators assigned a deviation category and provided a description of the specific deviation. However, the data monitoring plan did not specify protocol deviations without a categorical assignment should be queried. This resulted in some of the listed protocol deviations not having a corresponding categorical assignment.
- Missing deviation categories were assigned post-hoc based on the description provided by the Investigators. A revised Table 14.1.11 Summary of Protocol Deviations/Violations and Listing 16.2.27 Protocol Violations/Deviations were provided.

A summary of protocol violations/deviations is presented in Table 16. The values presented in the "Double-Blind" column refer to all protocol violations/deviations experienced by patients who enrolled in the double-blind period, regardless of whether the deviation occurred in the double-blind period (i.e., patients who had a protocol deviation in both the titration period and the double-blind period were counted in each of the "Total" and "Double-Blind" columns. The three most common protocol violations/deviations categories for the "Total" population and the "Double-Blind" populations were e-diary assessments, dosing deviations, and non e-diary related or missed protocol assessments. Only one patient (110003) was discontinued from the study because of protocol violations/deviations. This patient was found to be deceitful about cancer diagnosis, and in fact did not have cancer; discontinuation from the study occurred during the open-label dose-titration period.

Table 16: Summary of protocol deviations/violations

Deviations/Violations Categories*	Total (N=130) n (%)	Double-Blind** (N=98) n (%)
Subject inclusion and exclusion criteria	9 (6.9%)	7 (7.1%)
Subject informed consent procedures	3 (2.3%)	2 (2.0%)
Non e-diary related or missed protocol assessments	28 (21.5%)	20 (20.4%)
Dosing	53 (40.8%)	44 (44.9%)
Visits Timing/Out of Window	12 (9.2%)	6 (6.1%)
e-diary assessments	71 (54.6%)	61 (62.2%)
Labs	11 (8.5%)	10 (10.2%)
Other	25 (19.2%)	20 (20.4%)
Not Applicable	1 (0.8%)	1 (1.0%)

* A subject may be counted under multiple deviations/violations categories.
** All deviations/violations during the study were summarized for double-blind subjects.

Source: Table 14.1.11, Sequence 0016, page 3/3 of pdf.

Treatment compliance

The Applicant indicated (Table 13: Reason for discontinuation) a total of two patients were withdrawn from the trial because they failed to comply with the administrative requirements of the protocol; one patient (137002) was withdrawn during the open-

label, dose-titration period and one patient (119004) was withdrawn during the double-blind placebo-controlled crossover period.

The Applicant indicated that one of the patients (108001) who was discontinued early from the trial in the "Other" category was non-compliant. An information request was sent to the Applicant for clarification of the apparent dual categorization of patient 108001. The Applicant responded "…did not comply with drug dosing instructions and did not enter data in the electronic diary… the investigator's judgment, the Other category was more appropriate…." The Applicant's response suggested this situation was a compliant issue rather than "Other."

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint: Sum of Pain Intensity Differences at 30 Minutes (SPID30)

The statistical review was conducted by Yan Zhou, PhD. Please see Dr. Zhou's review for further details.

The SPID30 analysis excluded 6 patients from the 98 randomized patients in the double-blind placebo-controlled crossover period: two patients (114001 and 119003) had electronic diary malfunction and did not have reliable pain data and four patients (119004, 122008, 127003, and 135002) did not have at least one episode treated with FSS and at least one episode treated with placebo. This resulted in 92 patients (95.8%) being considered to be "evaluable" and being included in the SPID30 analysis.

The SPID30 analysis was preceded by a data reduction algorithm and was summarized over FSS-treated and placebo-treated breakthrough pain episodes within each patient. The difference within patient of the two SPID30 summaries was then calculated. In addition, within each patient, the mean baseline PI was calculated over all breakthrough pain episodes treated with study medication. Intra-patient SPID30 differences were then analyzed using analysis of co-variance (ANCOVA) using the Intra-patient mean baseline PI as a covariate.

The mean SPID at 30 minutes was greater for FSS-treated episodes (640.3) compared to the placebo-treated episodes (399.6) and the difference in treatments was statistically significant ($p < 0.0001$), Table 17. This indicated the overall degree of pain relief experienced by patients over that 30 minutes was significantly greater following FSS treatment.

Table 17: SPID30 "evaluable" population (N=92)

SPID30	FSS	Placebo	FSS minus Placebo	p-value*
Mean (SD)	640.3 (458.8)	399.6 (391.2)	240.7 (362.9)	<0.0001

Median Min, Max	555.1 -8, 2727	308.3 -100, 1948	201.0 -1020, 1055	

*Derived from ANCOVA with a dependent variable of SPID treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.

The Applicant's "evaluable" population consisted of patients who took at least one dose of study medication and had at least one pain measurement following administration of study medication, which was a modified ITT (mITT) population rather than an actual ITT population; the actual ITT population being all randomized patients who have received at least one dose of study drug and do not necessarily have to have had pain measurement following study drug administration. An information request was sent to the Applicant asking for an analysis of the primary efficacy endpoint using the actual ITT population and compare this result to the analysis submitted with the NDA. The Applicant submitted the requisite analysis that included the 6 patients who were excluded from the "evaluable" population. The analysis was performed based on two different estimation strategies:

- Assuming the difference between the FSS SPID30 and the Placebo SPID30 was equal to 0.0, and
- Assuming the difference between the FSS SPID30 minus the Placebo SPID30 score was equal to the worst possible FSS minus Placebo score observed in the trial at this time point. Patient 109010 had the worst score (FSS: 565 minus Placebo: 1585 = -1020) and this score (-1020) was assigned for the 6 patients who were excluded from the "evaluable" population.

The three analyses have been summarized in Table 18. The mean SPID30 was greater for FSS-treated episodes compared to the placebo-treated episodes and the difference in treatments was statistically significant for the actual ITT population, which was consistent with the mITT analysis. All analyses indicated the overall degree of pain relief experienced by patients over that 30 minutes was significantly greater following FSS treatment.

Table 18: Summary analysis of SPID30 by mITT and actual ITT population

Analysis	SPID30	FSS	Placebo	FSS minus Placebo	p-value***
mITT (N=92)	Mean (SD) Median Min, Max	640.3 (458.8) 555.1 -8, 2727	399.6 (391.2) 308.3 -100, 1948	240.7 (362.9) 201.0 -1020, 1055	<0.0001
*ITT (N=98)	Mean (SD) Median Min, Max	601.1 (470.4) 530.7 -8, 2727	375.1 (390.9) 280.4 -100, 1948	226.0 (356.3) 172.9 -1010, 1055	<0.0001
**ITT (N=98)	Mean (SD) Median Min, Max	635.7 (444.7) 561.1 -8, 2727	472.2 (474.5) 335.8 -100, 1948	163.6 (464.6) 172.9 -1010, 1055	<0.0001

*Assuming the difference between the FSS SPID30 and the Placebo SPID30 is equal to 0.0.
**Assuming the difference between the FSS SPID30 minus the Placebo SPID30 score was equal to the worst possible FSS minus Placebo score observed in the trial at this time point.
***Derived from ANCOVA with a dependent variable of SPID treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.

The Applicant also analyzed the SPID30 results for the following subgroups in the "evaluable" population:

- Age (<60 and ≥60 years, <65 and ≥65 years, and <75 and ≥75 years)
- Gender
- Race
- Type of around-the-clock pain relief medication used (ATCM)
- Type of prior BTCP medication used
- Successful dose of FSS

The Applicant reported descriptive statistics and p-value for each subgroup, and the results have been summarized in Table 19. There does not appear to be any significant differences in the subgroup analyses. However, the Applicant indicated "Of the subgroups analyzed, a potential difference between subgroups was noted only when age was evaluated at <65 and ≥65 years (p=0.1101, with any p-value <0.2 indicative of a potential difference)." This was a bit puzzling as p-value ≥0.05 is not considered significant.

Table 19: SPID30 "evaluable" population (N=92) subgroup analysis

Subgroup	N	Least Square Means	Standard Errors	P-value
Age (yrs)				
<60	67	363.3	44.5	0.3525
≥60	25	180.4	74.6	
<65	76	270.0	41.2	0.1101
≥65	16	101.9	93.7	
<75	89	243.4	38.3	0.7199
≥75	3	163.1	219.1	
Gender				
Male	43	263.1	38.3	0.5789
Female	49	221.2	219.1	
Race				
Caucasian	83	379.8	141.9	0.2921
Black	7	226.8	40.7	
Other	2	-17.7	215.0	
Around-the-clock medication				
Oral opioid	87	246.5	38.1	0.5107

Non-oral opioid	41	211.5	62.1	
Non-opioid	7	121.4	133.4	
Other	31	294.0	69.6	
BTCP medication				
Oral opioid	83	196.1	52.0	0.5254
Non-oral opioid	9	108.1	125.6	
Non-opioid	4	179.9	184.2	
Other	7	367.9	140.7	
FSS (mcg)				
100	4	131.7	180.9	0.3160
200	6	-17.8	146.8	
400	14	284.7	95.3	
600	14	208.7	96.1	
800	22	373.3	75.9	
1200	20	191.7	79.9	
1600	12	231.1	104.3	

The Applicant also provided sensitivity analyses; the SPID30 was calculated for the "evaluable" population by excluding any out-of-sequence FSS device numbers as well as by mITT and actual ITT populations. A similar statistically significant treatment difference ($p < 0.0001$) was observed between FSS- and placebo-treated episodes in these three population (Table 20). This data indicate that the finding of significantly superior efficacy for FSS compared with placebo on the primary efficacy endpoint is highly robust.

Table 20: Sensitivity analysis summary of SPID30

Analysis	SPID30	FSS	Placebo	FSS minus Placebo	p-value*
Excluded out of sequence device numbers (N=92)	Mean (SD) Median Min, Max	646.3 (479.1) 555.1 -8, 2727	402.3 (393.7) 317.5 -100, 1948	244.0 (374.9) 198.4 -1020, 1432	<0.0001
**ITT (N=98)	Mean (SD) Median Min, Max	601.1 (470.4) 530.7 -8, 2727	375.1 (390.9) 280.4 -100, 1948	226.0 (356.3) 172.9 -1010, 1055	<0.0001
***ITT (N=98)	Mean (SD) Median Min, Max	635.7 (444.7) 561.1 -8, 2727	472.2 (474.5) 335.8 -100, 1948	163.6 (464.6) 172.9 -1010, 1055	<0.0001

*Derived from ANCOVA with a dependent variable of SPID treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.

**Assuming the difference between the FSS SPID30 and the Placebo SPID30 is equal to 0.0.
***Assuming the difference between the FSS SPID30 minus the Placebo SPID30 score was equal to the worst possible FSS minus Placebo score observed in the trial at this time point.

6.1.5 Analysis of Secondary Endpoints(s)

The following Tables and Figures summarize the descriptive statistics and p-values for the following secondary endpoints:

- Table 21: Mean SPID by Time Point (ITT population)
- Figure 10: SPID (mean ± SE) after FSS and Placebo Administration (ITT Population)
- Table 22: Mean Total Pain Relief[1] by Time Point (ITT population)
- Figure 11: Total Pain Relief Scores (mean ± SE) after FSS and Placebo Administration (ITT Population)
- Table 23: Mean Patient Global Evaluation of Study Medication by Treatment
- Figure 12: PI Score (mean ± SE) after FCNS and Placebo Administration (ITT Population)
- Table 24: Mean PID[1] by Treatment and Time Point (ITT population)
- Figure 13: Pain Relief Scores (mean ± SE) after FSS and Placebo Administration (ITT Population)

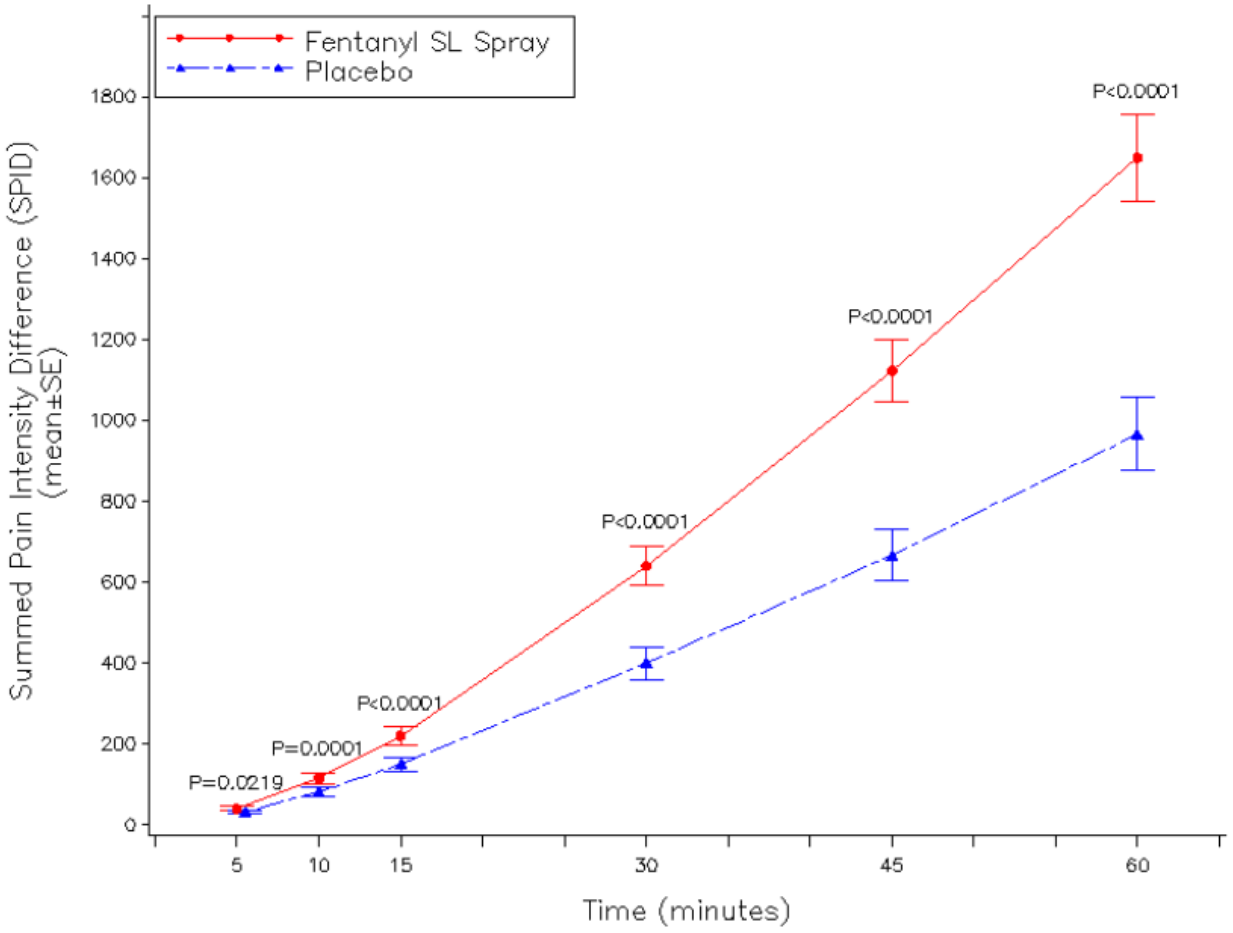
Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 100, where 0 represented “no pain” and 100 represented “worse possible pain.” P-values were obtained from an ANCOVA model performed separately at each time point. While the Applicant’s p-values are shown, there was no correction for multiple comparisons done except the p-values for the two secondary endpoints, TOTPAR30 and patient’s global evaluation of study medication at 30 minutes, were adjusted using the method of Hochberg.

Table 21: Mean SPID by time point “evaluable” population (N=92)

Secondary Endpoint	FSS (SD)	Placebo (SD)	FSS minus Placebo (SD)	p-value*
SPID 5	40.3 (57.7)	32.0 (52.1)	8.3 (34.1)	0.0219
SPID 10	115.0 (130.7)	81.1 (108.0)	34.0 (81.1)	0.0001
SPID 15	220.6 (209.7)	150.3 (172.5)	70.3 (140.5)	<0.0001
SPID 30	640.3 (458.8)	399.6 (391.2)	240.7 (362.9)	<0.0001
SPID 45	1122.0 (731.9)	667.0 (614.5)	454.9 (626.9)	<0.0001
SPID 60	1649.0 (1016.2)	965.7 (862.1)	638.3 (905.2)	<0.0001

*Derived from ANCOVA with a dependent variable of SPID treatment difference and covariate of patient’s mean baseline pain intensity values over all treated episodes.

Figure 10: SPID (mean ± SE) after FSS and placebo "evaluable" population (N=92)



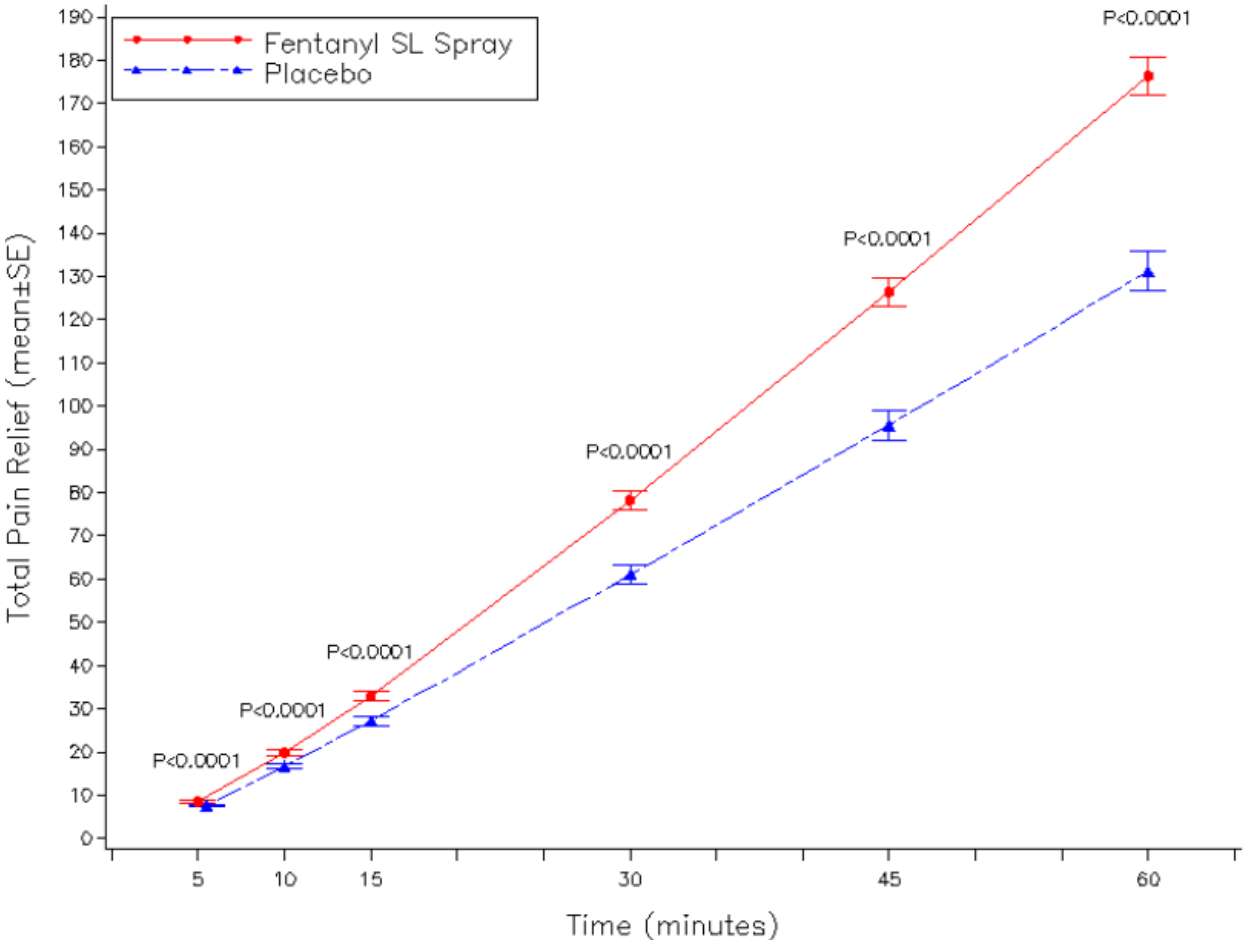
Source: INS-05-001 body FINAL STUDY REPORT, page 365/397 of the pdf

Table 22: Mean Total Pain Relief1 by time point "evaluable" population (N=92)

Secondary Endpoint	FSS (SD)	Placebo (SD)	FSS minus Placebo (SD)	p-value*
TOTPAR 5	8.6 (3.5)	7.6 (3.3)	1.0 (2.2)	<0.0001
TOTPAR 10	19.7 (7.0)	16.7 (6.5)	3.0 (4.7)	<0.0001
TOTPAR 15	32.9 (10.3)	27.1 (10.0)	5.8 (7.8)	<0.0001
TOTPAR 30**	78.3 (20.4)	61.0 (20.8)	17.3 (19.5)	<0.0001**
TOTPAR 45	126.3 (30.9)	95.5 (32.0)	30.8 (33.0)	<0.0001
TOTPAR 60	176.4 (41.5)	131.2 (43.6)	45.2 (46.8)	<0.0001

[1]Total pain relief was calculated as the weighted sum of the pain relief of all time points at or before the time point of interest.
*Derived from ANCOVA with a dependent variable of TOTPAR treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.
**The p-value for TOTPAR30 was adjusted for multiplicity using Hochberg's method.

Figure 11: Total Pain Relief Scores (mean ± SE) after FSS and placebo "evaluable" population (N=92)



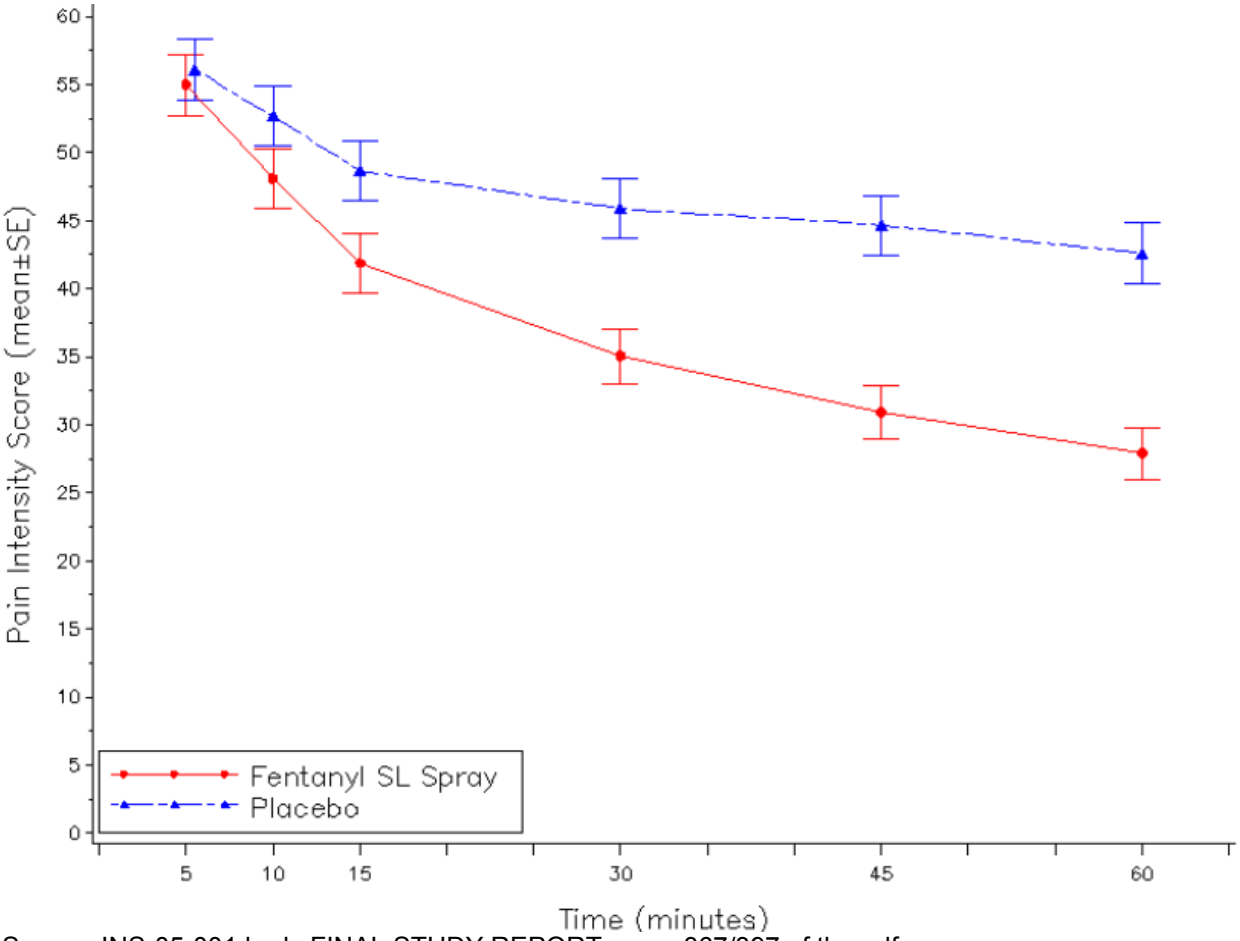
Source: INS-05-001 body FINAL STUDY REPORT, page 366/397 of the pdf

Table 23: Mean Patient Global Evaluation of study medication by treatment

Secondary Endpoint	FSS (SD)	Placebo (SD)	FSS minus Placebo (SD)	p-value*
Patient Global 30 min**	2.8 (0.8)	2.0 (0.8)	0.8 (0.6)	<0.0001**
Patient Global 60 min	3.1 (0.8)	2.2 (0.8)	0.9 (1.0)	<0.0001

*Derived from ANCOVA with a dependent variable of Patient Global Evaluation (XX minutes) treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.
**The p-value for patient global evaluation scores at 30 minutes was adjusted for multiplicity using Hochberg's method.

Figure 12: PI Score (mean ± SE) after FSS and placebo "evaluable" population (N=92)



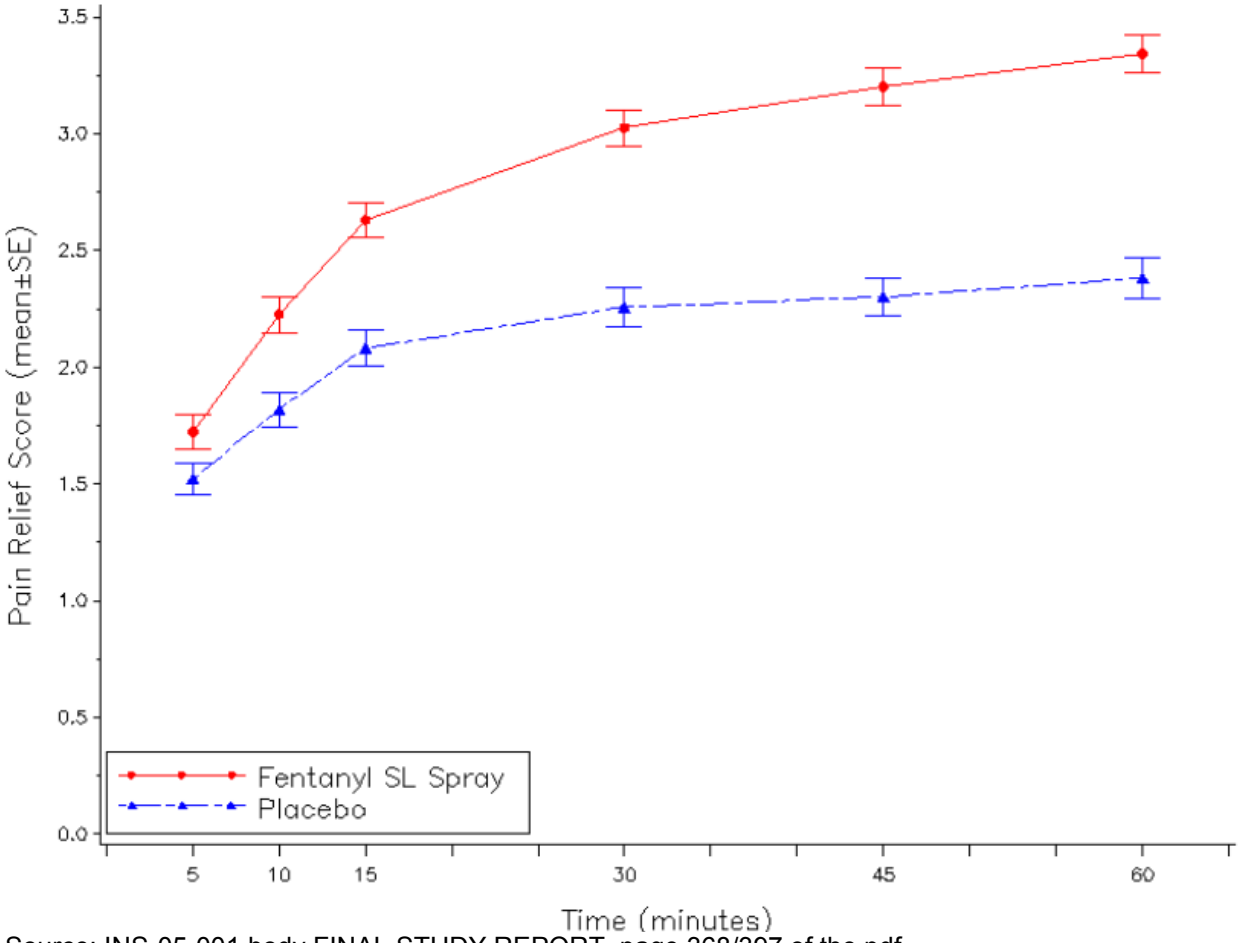
Source: INS-05-001 body FINAL STUDY REPORT, page 367/397 of the pdf

Table 24: Mean PID1 by Treatment and time point "evaluable" population (N=92)

Secondary Endpoint	FSS (SD)	Placebo (SD)	FSS minus Placebo (SD)	p-value*
PID 5	8.1 (11.5)	6.4 (10.4)	1.7 (6.8)	0.0219
PID 10	14.9 (15.0)	9.8 (12.1)	5.1 (10.6)	<0.0001
PID 15	21.1 (16.7)	13.8 (13.9)	7.3 (13.0)	<0.0001
PID 30	28.0 (17.7)	16.6 (15.9)	11.4 (16.1)	<0.0001
PID 45	32.1 (19.4)	17.8 (15.9)	14.3 (18.6)	<0.0001
PID 60	35.1 (20.4)	19.9 (17.9)	15.2 (19.5)	<0.0001

[1]Pain intensity difference was calculated as the baseline pain score minus the pain score at the specified time point.
*Derived from ANCOVA with a dependent variable of PID treatment difference and covariate of patient's mean baseline pain intensity values over all treated episodes.

Figure 13: Pain Relief Scores (mean ± SE) after FSS and placebo "evaluable" population (N=92)



Source: INS-05-001 body FINAL STUDY REPORT, page 368/397 of the pdf

Analyses of all of the above secondary endpoints support the primary efficacy finding for FSS. The mean SPID by time point showed positive results at 5, 10, 15, 30, 45, and 60 minutes. The mean PID, PR, and TOTPAR all showed significant differences between placebo and study drug at 5, 10, 15, 30, 45, and 60 minutes.

Overall satisfaction

Patients were instructed to complete the TSQM in reference only to FSS at the beginning (baseline) and at the end of the open-label dose-titration period (first visit of the double-blind, placebo-controlled crossover period). The TSQM category scores for effectiveness, side effects, convenience, and overall satisfaction range from 0 to 100 with higher scores indicating greater treatment satisfaction. Summaries of TSQM results were based on the safety population and only descriptive statistics were presented (Table 25) because assessments were completed prior to patient randomization. Improvements were observed across all categories at the end of the open-label dose-titration period with 89% of the patients indicating they were satisfied, very satisfied or extremely satisfied with FSS compared with 41% of patients at baseline (Table 26).

Table 25: TSQM safety population – Baseline and change from baseline

	Open-Label Titration Visit (Baseline)	Double Blind (DB) Visit	DB Change From Baseline
Effectiveness			
n	128	96	96
Mean	48.8	75.2	26.1
Median	50.0	78.0	27.0
SD	18.2	14.0	20.9
Min, Max	0, 100	33, 100	-28, 67
Side Effects			
n	128	95	95
Mean	78.4	91.3	12.5
Median	100.0	100.0	0.0
SD	28.2	18.1	30.8
Min, Max	0, 100	6, 100	-94, 100
Convenience			
n	128	95	95
Mean	66.2	74.0	8.0
Median	67.0	78.0	11.0
SD	16.3	15.3	21.2
Min, Max	17, 100	39, 100	-50, 50
Global Satisfaction			
n	128	95	95
Mean	55.1	75.4	20.5
Median	57.0	79.0	22.0
SD	21.0	16.3	23.1
Min, Max	0, 100	21, 100	-50, 86

Source: INS-05-001 body FINAL STUDY REPORT, page 203/397 of the pdf

Table 26: Satisfaction with FSS

	Open-Label Titration Visit (Baseline)	Double Blind (DB) Visit
Satisfied with This Medicaiton	128	96
EXTREMELY DISSATISFIED	1 (1%)	0 (0%)
VERY DISSATISFIED	10 (8%)	0 (0%)
DISSATISFIED	17 (13%)	3 (3%)
SOMEWHAT SATISFIED	47 (37%)	7 (7%)
SATISFIED	33 (26%)	26 (27%)
VERY SATISFIED	13 (10%)	44 (46%)
EXTREMELY SATISFIED	7 (5%)	15 (16%)
INVALID	0 (0%)	0 (0%)
MISSING	0 (0%)	1 (1%)

Source: INS-05-001 body FINAL STUDY REPORT, page 208/397 of the pdf

The patient's global evaluation of their experience while taking study medication was assessed at 30 and 60 minutes following treatment for each BTCP episode that was assessed during the open-label dose-titration and double-blind, placebo-controlled crossover periods. Patients rated their overall impression using a 5-point categorical scale (1 = poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = excellent). The results have been summarized in Table 23. At 30 and 60 minutes the patient global evaluation was significantly improved ($p<0.0001$) when BTCP episodes were treated with FSS compared to placebo.

Responder analyses

The Applicant created four categories of responder analysis based on SPID scores from the "evaluable" population (N=92). The categories were unit change analysis for SPID, TOTPAR, PI, and PID. The analyses were conducted as post-hoc analysis. The data were presented as follow:

- A patient count categorized by the magnitude of the difference in placebo and FSS benefit (e.g., a placebo response of +40 and a FSS response of +61 is a 21 unit difference in favor of FSS). This was presented as 7 categories at each time point for each of the variables.
- A summary of the above illustrating the number of patients and percentage who benefited from FSS (50% is defined as no benefit versus placebo). A simple binomial p-value is presented as supporting evidence of the overall results from the corresponding pre-specified endpoint table. P-values were computed using one-sided binomial test (proportion = 0.5 vs. proportion > 0.5) for comparison of "FSS Better" versus "Same" and "Placebo Better."
- A summary of the number and percentage of patients who experienced a positive treatment benefit of ≥20 units, regardless of how they performed on the other treatment. P-values were computed using McNemar symmetry test for the 2 by 2 table of the joint FSS/Placebo response

Unit change analysis for SPID: The unit change analysis favoring FSS over placebo was observed at each time point from 5 minutes through 60 minutes. At SPID30, 79% of patients treated with FSS had improved SPID values ($p <0.0001$). When SPID5 values were used as baseline values to calculate the proportion of patients treated with FSS that experienced ≥20 SPID units from baseline, a greater proportion of patients treated with FSS experienced an absolute change of ≥20 SPID units than with placebo across all time points (e.g., SPID30: 99% of patients treated with FSS had ≥ 20 unit improvement compared with 89% of patients treated with placebo; $p=0.0027$).

Unit change analysis for TOTPAR: The unit change analysis favoring FSS over placebo was observed at each time point from 5 minutes through 60 minutes. At TOTPAR30, 82% of patients treated with FSS had improved TOTPAR values ($p <0.0001$). When TOTPAR5 values were used as baseline to calculate the proportion of patients treated

with FSS that experienced an absolute change of ≥ 20 TOTPAR units from baseline, the only time that favors FSS was TOTPAR15 (p<0.0001). For all other times there was no statistical significance.

Unit change analysis for PI: The unit change analysis for PI favoring FSS over placebo was observed at each time point from 5 minutes through 60 minutes. At PI30, 78% of patients treated with FSS had improved PI values (p <0.0001). The proportion of patients experiencing an absolute change of ≥20 PI units from baseline was calculated for both FSS and placebo. There was no demonstrable statistical difference at PI 5 minutes. However, a greater proportion of patients treated with FSS experienced a ≥ 20 unit improvement in pain intensity values from PI10 through PI60.

Unit change analysis for PI: The unit change analysis for PID favoring FSS over placebo was observed at each time point from 5 minutes through 60 minutes. At PID30, 80% of patients treated with FSS had improved PID values (p <0.0001). When PID5 values were used as baseline to calculate the proportion of patients treated with FSS that experienced an absolute change of ≥20 PID units from baseline, there was no demonstrable statistical difference at PID10. However, a greater proportion of patients treated with FSS experienced a ≥20 unit improvement in PID from PID15 through PID60.

Cumulative responder analysis

There was no cumulative or continuous responder analysis.

Use of rescue medication

The Applicant provided three analyses of rescue medication use by treatment groups; incidence of rescue medication usage, bivariate discrete distributions of the number of BTCP episodes for each patient treated with FSS or placebo that required rescue medication, and a hazard analysis of the time to rescue medication usage.

The incidence of rescue medication use during a BTCP episode was compared between treatment groups using a generalized estimation equation (GEE) model for repeated measure within patients, and the results appear in Table 27. Within 60 minutes of study medication, rescue medication was used for 10% of the episodes treated with FSS whereas rescue medication was used for 28% of the episodes treated with placebo. Rescue medication use was significantly lower following FSS than with placebo (p<0.0001).

Table 27: Incidence of rescue (supplemental) medication use

	Fentanyl SL Spray (N=92)	Placebo (N=92)	p-value*
Incidence of Supplemental Medication Use**			<.0001
n	92	92	
Mean	0.10	0.27	
Median	0.00	0.00	
SD	0.16	0.32	
Min, Max	0.0, 0.7	0.0, 1.0	

* p-value for a treatment difference based on the score statistic in a Type 3 generalized estimating equation model for repeated measures (Proc Genmod in SAS) with a binomial dependent variable (yes/no) of supplemental medication use for each treated episode.
** Derived separately for each subject and treatment as the # of episodes requiring supplemental medication divided by # of episodes treated.

Source: INS-05-001 body FINAL STUDY REPORT, page 200/397 of the pdf

Bivariate discrete distributions of the number of BTCP episodes for each patient treated with FSS or placebo and required rescue medication was tabulated in Table 28 by the following intervals: 0 or no use of supplemental medication, >0 to 0.15, >0.15 to 0.3, >0.3 to 0.45, >0.45 to 0.6, >0.6 to 0.75, and >0.75 to 1. There were 39 patients who did not require rescue medication within 60 minutes of treatment. There were 19 patients treated with FSS that did not require rescue medication, but required rescue medication when treated with placebo with an incidence of >0.3. The incidence of rescue medication use increased when patients used placebo to treat their BTCP.

It would be more informative to have an analysis of the data set for the number of episodes in which rescue medication was used within 30 within 60 minutes by treatment groups.

Table 28: Bivariate distribution of BTCP episodes treated with FSS or placebo requiring rescue medication

	Fentanyl SL Spray						
Placebo	0	>0 - 0.15	>0.15 - 0.3	>0.3 - 0.45	>0.45 - 0.6	>0.6 - 0.75	>0.75 - 1
0	39	3	2	2	1		
>0 - 0.15							
>0.15 - 0.3							
>0.3 - 0.45	12	6	2				
>0.45 - 0.6	1						
>0.6 - 0.75	4	7	4	2	1	1	
>0.75 - 1	2	1	1			1	

Incidence of supplemental medication use derived separately for each subject and treatment as the # of episodes requiring supplemental medication divided by # of episodes treated.
Note: Percentage is based on 92 subjects in Fentanyl SL Spray and 92 subjects in Placebo groups.

Source: INS-05-001 body FINAL STUDY REPORT, page 201/397 of the pdf

A hazard analysis of the time to rescue medication use was summarized in Table 29. Within each episode, the time to rescue medication use was compared between treatment groups using a Cox Proportional Hazards model to account for the clustering of multiple episodes within a patient. The hazard ratio was 0.33 (CI 0.24, 0.45), which indicates the likelihood of rescue medication use was reduced by 67% when BTCP was treated with FSS than with placebo.

Table 29: Hazard analysis of time to rescue medication usage

	Results
Time to Supplemental Medication Use (minutes)	
p-value	<.0001
Hazard ratio	0.33
95% Confidence interval	(0.24, 0.45)

Results are from a Cox proportional hazards model accounting for the clustering of multiple episodes within subject. P-value for treatment effect and confidence interval are from the Wald Statistic using the sandwich estimate of the covariance matrix.

Source: INS-05-001 body FINAL STUDY REPORT, page 202/397 of the pdf

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimen used during the clinical study was appropriate to support efficacy and as discussed below, safe use, and will be the dosing recommendation in labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy was persistent throughout the study duration. Patients were already tolerant to opioids for enrollment into the study. This study did not assess the development of additional tolerance related to study drug.

6.1.10 Additional Efficacy Issues/Analyses

Discussion of Efficacy Findings

I. The Applicant's analysis of the primary endpoint (SPID30) for Study INS-05-001, as confirmed by Dr. Yan Zhou, FDA statistician of the Division of Biometrics, supports the finding of efficacy for FSS compared to placebo ($p < 0.0001$) for the treatment of breakthrough pain in patients with malignancies receiving around-the-clock opioid therapy for cancer pain.
II. The secondary endpoints analyses, except for TOTPAR30 and patient's global evaluation, were not adjusted for multiple comparisons. However, due to their consistent trends in favor of FSS compared to placebo, they support the conclusion that patients receiving FSS experienced greater pain relief and less pain intensity than those who received placebo.
III. [redacted] (b) (4)
IV. Protocol deviations
V. The Applicant's analyses of rescue medication use were complicated, and indicate rescue medication use within 60 minutes of study medication was significantly less following FSS than with placebo treatment. It would be more

informative to have an analysis of the data set for the number of patients who used rescue medication and the number of episodes in which rescue medication was used within 30 and 60 minutes by treatment groups.

7 Review of Safety

Safety Summary

Review of the available safety data indicates that the adverse event profile for FSS is consistent with what is known for transmucosal immediate-release fentanyl products used to treat breakthrough pain in opioid tolerant cancer patients on around the clock opioid therapy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Six clinical (three Phase 1 and three Phase 3) studies have been conducted with FSS with a total patient exposure of 490 (Table 30), however, the two Phase 3 multiple-dose FSS studies INS-05-001 and INS-06-007 form the basis for safety assessment of FSS.

Table 30: Clinical studies

Study	Number of patients	Number exposed to FSS
FNY-P4-270* (Phase 1)	9	6
INS-06-003 (Phase 1)	40*	40
INS-06-004 (Phase 1)	67*	67
INS-09-011 (Phase 3)	18	18
INS-05-001 (Phase 3)	130	130
INS-06-007 (Phase 3)	229	229
Total	493	490

FNY-P4-270* was a single-blind, placebo-controlled, sequential single ascending dose study in healthy adult male subjects to determine pharmacokinetics, safety and tolerability of FSS under fasting conditions. The study medications were FSS were 100, 400, 800 mcg or placebo. There were a total of 9 subjects enrolled; 6 received FSS and 3 received placebo. Subjects were not pre-treated with naltrexone.

INS-06-003 was an open-label, randomized, single-dose, 3-period, 3-treatment crossover study comparing absorption and bioavailability of FSS to Actiq and IV fentanyl citrate under fasting conditions in healthy adult subjects. The study medications were

FSS 400 mcg, Actiq 400 mcg, and IV fentanyl citrate 100 mcg. There were a total of 40 subjects enrolled and all the subjects were pre-treated with naltrexone.

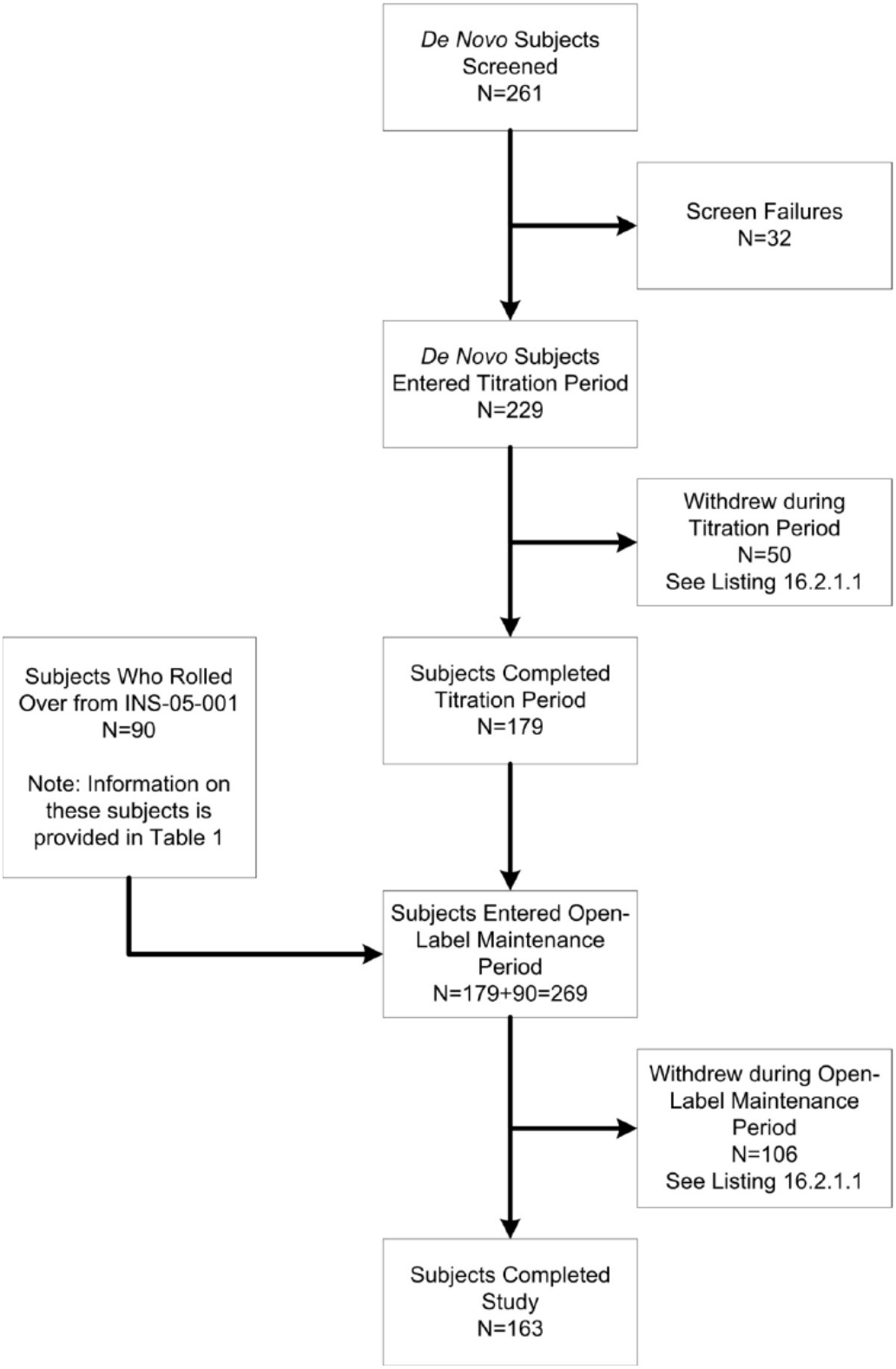
INS-06-004 was a two part open-label study in healthy adult subjects. Part A was a single dose, five-treatment (FSS 100, 200, 400, 600, and 800 mcg), five-sequence, five-period crossover comparative pharmacokinetic study under fasted conditions. Part B was a single-dose, five-treatment, two sequence, five-period crossover study to assess the effect of temperature and pH in the oral cavity on the relative bioavailability of FSS 200 mcg. There were a total of 67 subjects enrolled; 53 in Part A and 14 in Part B. All the subjects were pre-treated with naltrexone.

INS-09-011 was an open-label single FSS dose (100 mcg) pharmacokinetic study in opioid-tolerant cancer patients with and without oral mucositis with BTCP. There were a total of 18 patients enrolled; 9 with mucositis and 9 without mucositis.

INS-05-001 was a randomized, double-blind, placebo-controlled, multiple cross-over study comparing FSS with placebo for the treatment of BTCP in adult cancer patients on a stable opioid regimen for persistent pain as described in Section 5

INS-06-007 was an open-label study evaluating the safety of FSS for the treatment of BTCP in adult cancer patients on a stable opioid regimen for persistent pain. Patients were eligible to enter this study following successful completion of INS-05-001, or directly if they met the same entry criteria as INS-05-001. Patients directly entering this study are titrated to an effective dose (100 to 1,600 mcg per dose) in a similar manner to the one used in INS-05-001. Patients who could be titrated to an effective and tolerable FSS dose continued at that dose for up to 90 days. The Study Team had daily telephone contact with the patients during the course of the study to mange their electronic diaries and to respond to study medication questions. The Investigator had the option to conduct unscheduled visits to include additional assessments as needed. Safety and tolerability were evaluated by AEs, vital signs, laboratory investigations, evaluation and examination of the oral cavity, and physical examination. There were 261 patients who were screened and 229 (de novo) patients were eligible to enter the titration period with 179 patients completing this period and going onto the maintenance period. The maintenance period comprised of the 179 patients who completed the titration period and the 90 patients rolled over from study INS-05-001; total of 269 patients. Of the 269 patients, 163 completed the study. Figure 14 is a patient disposition flow diagram.

Figure 14: Patient disposition INS-06-007



Source: Response to request for clinical information, 1.11.3 efficacy information amendment, page 6/8 of the pdf.

Patient disposition for the titration period is summarized in Table 31 and patient disposition for the maintenance period is summarized in Table 32. The three most common reasons for withdrawal from the study during the titration period were patient decision (19/229; 8%), AEs/SAEs (11/229; 5%), and intercurrent illness, AE or surgery (5/229; 2%). The most common reasons for withdrawal from the study during the maintenance period were AEs/SAEs (60/269; 22%), patient decision (21/269; 8%), and intercurrent illness, AE or surgery (13/269; 5%).

Table 31: Patient disposition – titration period

	100 n (%)	200 n (%)	400 n (%)	600 n (%)	800 n (%)	1200 n (%)	1600 n (%)	Total n (%)
Entered the Period	88	43	26	16	20	18	18	229
Completed the Period	45 (51.1%)	41 (95.3%)	26 (100%)	16 (100%)	20 (100%)	18 (100%)	18 (100%)	184 (80.3%)
Withdrew from the Period	43 (48.9%)	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	45 (19.7%)
Reason for withdrawal								
AEs/SAEs[1]	11 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (4.8%)
Failure to comply with protocol[2]	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Intercurrent illness, AE or surgery	5 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.2%)
Investigator decision	3 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
Other	1 (1.1%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
Significant protocol violation	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Subject decision for withdrawal	18 (20.5%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (8.3%)
Symptoms/signs of possible toxicity	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Successful dose not determined[3]	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)

All percentages are based on the number of subjects who entered the period.
[1] That contraindicated further administration of the study drug
[2] Specifically the administrative conditions
[3] During the titration period

Source: INS-06-007 body FINAL STUDY REPORT, page 62/808 of the pdf.

Table 32: Patient disposition – maintenance period

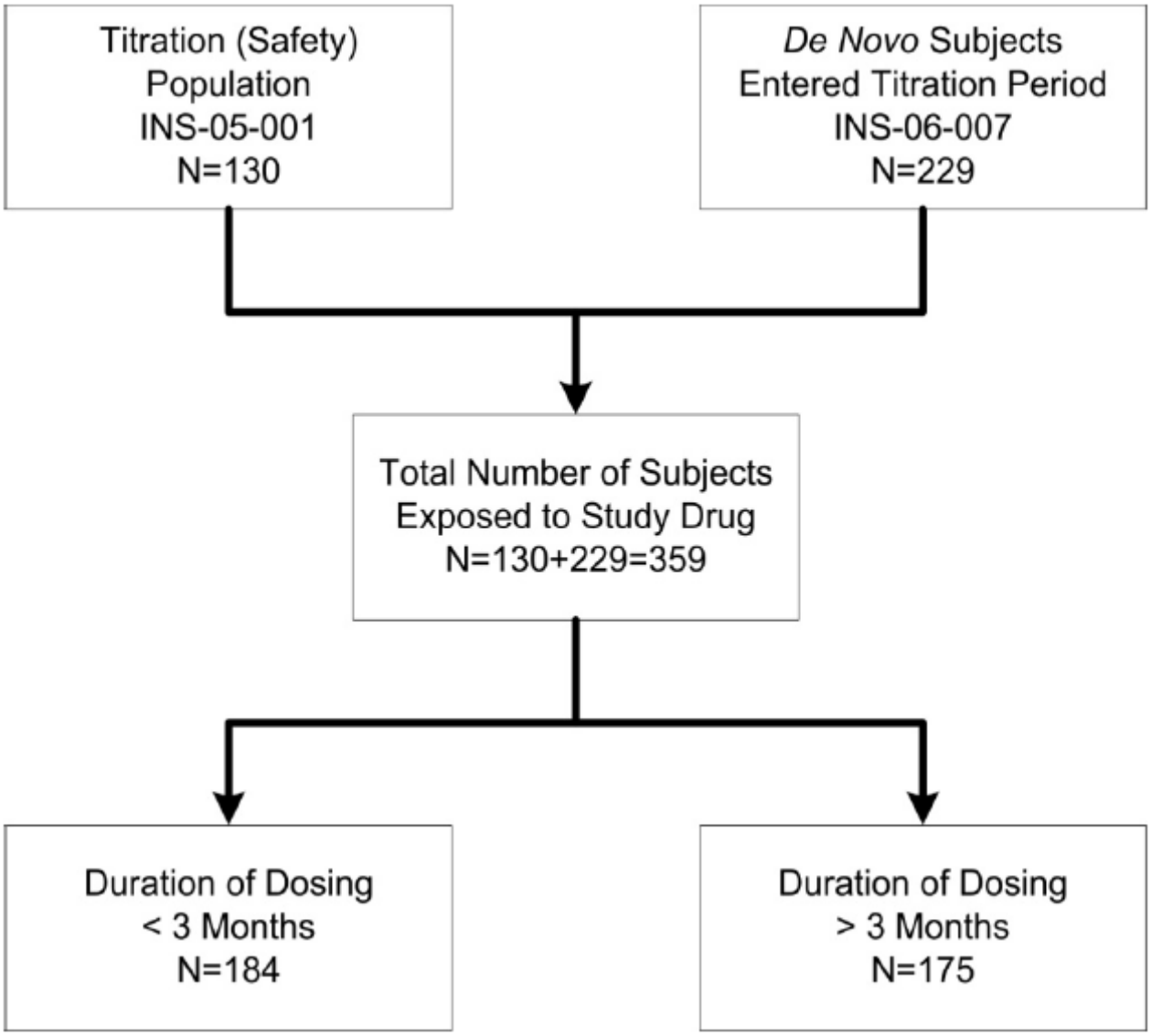
	100 n (%)	200 n (%)	400 n (%)	600 n (%)	800 n (%)	1200 n (%)	1600 n (%)	Total n (%)
Entered the Period	42	45	42	29	34	42	35	269
Roll-over from Efficacy Portion of Study	4 (9.5%)	6 (13.3%)	13 (31.0%)	12 (41.4%)	19 (55.9%)	19 (45.2%)	17 (48.6%)	90 (33.5%)
Completed the Period	19 (45.2%)	25 (55.6%)	30 (71.4%)	16 (55.2%)	19 (55.9%)	26 (61.9%)	28 (80.0%)	163 (60.6%)
Withdrew from the Period	23 (54.8%)	20 (44.4%)	12 (28.6%)	13 (44.8%)	15 (44.1%)	16 (38.1%)	7 (20.0%)	106 (39.4%)
Reason for withdrawal								
AEs/SAEs[1]	15 (35.7%)	11 (24.4%)	5 (11.9%)	5 (17.2%)	11 (32.4%)	9 (21.4%)	4 (11.4%)	60 (22.3%)
Failure to comply with protocol[2]	0 (0.0%)	1 (2.2%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.1%)
Intercurrent illness, AE or surgery	4 (9.5%)	1 (2.2%)	2 (4.8%)	2 (6.9%)	1 (2.9%)	2 (4.8%)	1 (2.9%)	13 (4.8%)
Investigator decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	3 (1.1%)
Other	1 (2.4%)	1 (2.2%)	2 (4.8%)	1 (3.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	6 (2.2%)
Subject decision for withdrawal	3 (7.1%)	6 (13.3%)	3 (7.1%)	2 (6.9%)	1 (2.9%)	4 (9.5%)	2 (5.7%)	21 (7.8%)

[1] That contraindicated further administration of the study drug
[2] Specifically, the administrative conditions

Source: INS-06-007 body FINAL STUDY REPORT, page 63/808 of the pdf.

The contribution of the two Phase 3 multiple-dose FSS studies INS-05-001 and INS-06-007 that form the basis for the safety assessment of FSS is shown in Figure 15. The total number of patients in the safety data base was 359; 130 from INS-05-001 and 229 from INS-06-007.

Figure 15: Multiple-dose FSS studies – basis for FSS safety assessment



Source: Response to request for clinical information, 1.11.3 efficacy information amendment, page 7/8 of the pdf.

120-day safety update (Amendment 0011) was submitted by the Applicant on 07 July 2011, acknowledging that all clinical studies conducted with FSS were completed before the 04 March 2011 NDA submission and there are no updates to the safety information previously provided in NDA 202-788 (0000). This safety update does not change my overall impression of the adverse event profile of FSS.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 10.1. 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

The Applicant pooled the data from studies INS-05-001 and INS-06-007, and the four pharmacokinetic studies (INS-09-011, FNY-P4-270, INS-06-003, INS-06-004). The information from the pooled pharmacokinetic studies data set is limited by the diversity of the study designs; one study was conducted in opioid-tolerant cancer patients, one study was conducted in healthy volunteers, and two studies were conducted in healthy volunteers pre-treated with naltrexone.

7.2 Adequacy of Safety Assessments

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

There was a total of 490 adults exposed to FSS in all studies. A total of 113 healthy volunteer subjects were enrolled in Phase 1 studies, most of whom received naltrexone and so, are not included in the safety assessments of FSS. A total of 377 opioid-tolerant cancer patients were enrolled in Phase 3 studies. Of the 377 patients in the Phase 3 studies, there were 18 patients with oral mucositis who received a single FSS dose in Study INS-09-011, and the safety of these patients is considered separately from the patients without oral mucositis. There were 359 patients enrolled in multiple-dose studies of FSS that comprise the bulk of the safety database with FSS as described in Table 33. A total of 175 patients were exposed to FSS for at least 3 months, and 61% of patients were treated with the highest dose for at least three months.

Table 33: Duration of FSS exposure by dose in cancer patients – multiple-dose FSS studies (INS-05-001 and INS-006-007)

	Number (%) of patients exposed at any dose within specified duration

Patients	Day 1 to < 1 mos	1 mos to < 2 mos	2 mos to < 3 mos	≥3 mos
N=359 (Total)	110 (31)	39 (11)	35 (10)	175 (49)
Dose	Number (%) of patients exposed at specific dose within specified duration (patients may be exposed to more than one dose and/or duration)			
100 mcg (N=45)	13 (29)	5 (11)	8 (18)	19 (42)
200 mcg (N=50)	13 (26)	5 (10)	10 (20)	22 (44)
400 mcg (N=47)	8 (17)	8 (17)	6 (13)	25 (53)
600 mcg (N=36)	8 (22)	5 (14)	13 (36)	10 (28)
800 mcg (N=48)	14 (29)	9 (19)	7 (15)	18 (38)
1200 mcg (N=48)	11 (23)	10 (21)	8 (17)	19 (40)
1600 mcg (N=38)	8 (21)	4 (11)	3 (8)	23 (61)

Source: Modified from ISS, module 5.3.5.3.28 page 49-50/2947 of pdf.

The demographic data for the multiple-dose FSS Phase 3 studies demonstrate the majority of the patients were Caucasian (71%). The mean age was 55 years (24-92 years) and equally divided between male and female. The average weight was 72 kg. Table 34, summarizes the demographics of patients from studies INS-05-001 and INS-006-007.

Table 34: Demographics of the cancer patients from the multiple-dose FSS studies (INS-05-001 and INS-006-007)

	Total (N=359)
Age (years)	
Mean (SD)	55.0 (12.4)
Median	54.7
Min, Max	24, 92
<65	281 (78.3)
≥65	78 (21.7)
<75	344 (95.8)
≥75	15 (4.2)
Gender, N (%)	
Male	173 (48.2)
Female	186 (51.8)
Race*, N (%)	

American Indian/Alaska Native	3 (0.8)
Asian	81 (22.6)
African American	16 (4.5)
Native Hawaiian/Pacific Islander	1 (0.3)
White	253 (70.5)
Other	6 (1.7)
Weight (kg)	
Mean (SD)	71.7 (22)
Median	68.5
Min, Max	31, 194

*A patient may be counted under multiple race categories.
Source: Modified from ISS, module 5.3.5.3.28 page 44-45/2947 of pdf.

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

There was no special animal or in vitro testing performed.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Dr. Wei Qiu's Clinical Pharmacology review for information regarding the metabolic, clearance and interactions of FSS. The Applicant did not perform specific studies addressing of metabolism or excretion of fentanyl used via sublingual route.

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

Since FSS 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

7.3.1 Deaths

Deaths during the clinical trials of FSS were expected due to the nature of the patient population (cancer patients, often terminal). A total of 92 (26%) deaths were recorded during the development program, all during the multiple-dose studies in cancer patients; three (1%) deaths were recorded during study INS-05-001 and 89 (25%) deaths were recorded during study INS-06-007. 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 INS-05-001 and open-label design of INS-06-007.

INS-05-001

There were three deaths recorded during this study. Two patients (105003 and 142012) died during the open-label period and one patient (119005) died during the double-blind period. The CRFs, data listings, and narratives were reviewed for each death. There was insufficient information to determine the cause of death to be related to study drug. The cause of death appeared to have been related to the patient's underlying progression of disease. The narratives of these deaths are summarized below:

Patient 105003 was a 66 year-old white male with a history of lung cancer with metastasis to the bone that was diagnosed in June 2007 and was treated with chemo- and radiation therapy. Other significant medical history included squamous cell head and neck cancer involving the tongue treated with chemo- and radiation therapy in 2005, hypothyroidism, and low back pain. His medications included morphine sulfate, gabapentin, methadone, levothyroxine, lactulose, vinorelbine, epoetin alfa, promethazine, multivitamin, ascorbic acid, macrogol, magnesium hydroxide, palonosetron, pemetrexed, and dexamethasone.

The patient entered the open-label titration period of the study on (b) (6), one week following his last round of chemotherapy. On (b) (6), the patient developed trouble walking, difficulty with coordination, and an unsteady gait with progressive ascending numbness.

On (b) (6) (8 days after the patient's first FSS dose and one day after his last FSS dose) the patient was admitted to a hospital with numbness from the waist down, inability to urinate, and worsening of his back pain. A work up revealed extensive metastatic disease involving multiple levels of the spine, chest and abdomen The patient was discharged from the hospital on (b) (6) to a skilled nursing facility and died on (b) (6).

FSS dosing was discontinued prior to the patient's hospitalization and the patient was discontinued from the study due to his overall poor prognosis. The patient's death appears to have been a result of progression of the underlying cancer and unrelated to study participation.

Patient 142012 was a 62 year-old white male with a history of pancreatic cancer and had received two chemotherapy treatments within the past 2.5 weeks. Other significant medical history included COPD, suspected Parkinson's, rheumatoid arthritis and sacral decubitus ulcer. His medications included fluticasone, ipratropium and albuterol, zolpidem, carbidopa and levodopa, lorazepam, ipratropium and salbutamol, diphenhydramine, oxycodone, fentanyl patch, furosemide, and hydroxyzine.

The patient entered the open-label titration period of the study on (b) (6), but took only a single FSS dose. The patient withdrew consent from the study on (b) (6). The details for withdrawal were unclear. The CRF indicated the primary reason for early termination was "subject decision for withdrawal." The patient died on (b) (6) 22 days after his first and only FSS dose. The patient's death appears to have been a result of progression of the underlying cancer and unrelated to study participation.

Patient 119005 was a 58 year-old African-American female with a history of cervical cancer that was diagnosed in 2007. Her medications included morphine, hydrocodone, oxycodone and acetaminophen, lorazepam, lansoprazole and senna.

The patient entered the open-label titration period of the study on (b) (6) She achieved a stable FSS dose of 1600 mcg on (b) (6) and entered the double-blind period of the study the following day.

On (b) (6) the patient experienced uncontrolled pain related to progression of her cervical cancer associated with dehydration. She was admitted to a hospital on an unknown date in (b) (6) and discharged on an unknown date. Subsequently, the patient was admitted to hospice care on an unspecified date and died on (b) (6) The patient's sister returned the study drug. The date of her last dose of study drug was unknown and the patient was discontinued from the study on an unknown date. The patient's death certificate was not available and no further details were available.

Although the temporal relation between the patient's last dose of study drug and her death is unknown, given this patient's medical history, her clinical course, and her admission to hospice care, this patient's death appears to be related to the progression of underlying cancer disease and does not appear to be related to study drug.

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There were 89 (25%) deaths recorded during this study; 10 deaths occurred during the titration period and 79 deaths during the maintenance period. The Applicant provided the CRFs and data listings for each death, and only provided one death narrative because it was the only death that was assessed by the Investigator to be possibly related to study drug. An information request was sent to the Applicant asking for narratives of all recorded deaths during this study.

The CRFs, data listings, and narratives were reviewed for each death. There were 77 patients who died of cancer progression and 12 who died of other reasons: sepsis (2), pulmonary embolism (2), cardiopulmonary arrest, cardiac failure, cardiac arrhythmia, aspiration pneumonia, intracranial hemorrhage, stroke, renal failure, and respiratory distress (aspiration). Of the 12 patients who died of other reasons, eight appeared to have died as a result of underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs (i.e., sepsis (2), pulmonary embolism (2), heart failure, intracranial hemorrhage, stroke, and renal failure) and unrelated to study participation. The remaining four deaths are of possible interest because of potential relation to study drug. In addition, there were two deaths (408004 and 411002) with information pertaining to the temporal relation between study drug dosing and death. The narratives of these deaths are as follow:

Patient 142009 was a 59 year-old white male with a history of thyroid cancer. Other significant medical history included nausea, vomiting, confusion, peripheral vascular disease, asthma/COPD, sleep apnea, fatigue, depression, low levels of calcium, total protein, and pancytopenia. His medications included morphine, hydromorphone, dexamethasone, omeprazole, citalopram, levothyroxine, prochlorperazine, sorafenib, levalbuterol, and furosemide.

The patient was rolled over from study INS-05-001 and entered the maintenance period on (b) (6) using a FSS dose of 800 mcg. Two weeks into the maintenance period the patient was hospitalized for aspiration pneumonia and shortness of breath. The patient died the next day.

The temporal relation between the patient's study drug dosing and vomiting/aspiration was unknown, and there was insufficient information in the CRF, data listing, and narrative to associate the cause of death with use of study drug. However, as the patient had tolerated study drug during study INS-05-001, it appears his death was due to his underlying malignancy and related complications.

Patient 413007 was a 41 year-old Asian female with a history of lung cancer. Other significant medical history included breast cancer with liver metastasis. Her medications included tramadol, hydrocortisone, cyclophosphamide, and doxorubicin.

This patient entered study INS-06-007 de novo on (b) (6) and began her FSS titration at 100 mcg. The next day she experienced vomiting and was transferred to a high dependency unit of the hospital. Two days into the titration period the patient refused study medication and did not progress to the maintenance period. On (b) (6) the patient had severe breathlessness and was transferred to the ICU where her treatment included hydrocortisone, aminophylline, morphine, isoniazid, acetaminophen, and saline nebulizers. The patient died the next day.

As it appears that the study drug was last given more than a day prior to the patient's death, it is unlikely that her death was related to the use of study drug.

Patient 400006 was a 38 year-old Asian female with breast cancer metastatic to the lung and pleura. She had undergone multiple cycles of radiation therapy and chemotherapy; last cycle of chemotherapy was approximately two weeks prior to study enrollment. Her medications included belladonna dry extract, caffeine, ergotamine tartrate, acetaminophen, morphine, gabapentin, etoricoxib, amitriptyline, chlordiazepoxide, diclofenac, fentanyl transdermal patch, and ketamine.

This patient entered study INS-06-007 de novo on (b) (6) and began her FSS titration at 100 mcg. She achieved a stable dose of 200 mcg two days later. Three days into her maintenance period the patient experienced severe pain and five days into the maintenance period the patient experienced breathlessness. She was diagnosed with disease progression and chest infection. The patient was discharged from the hospital against medical advice with ongoing breathlessness on (b) (6), and the last FSS dose was administered on the same day. The patient died of cardiopulmonary arrest the next day.

As the patient died the day following the last use of study medication, it is unlikely that her death was associated with the use of study drug.

Patient 142013 was a 65 year-old white male with a history of head and neck cancer. He had a variety of cancer related surgeries, radiation therapy, and chemotherapy. Other significant medical history included hypertension, hypercholesterolemia, back pain, hip pain, confusion, dysphagia, hoarseness, insomnia, weight fluctuations, fatigue, numbness in both hands, weakness, anemia, dehydration, nausea, thrush, vomiting, and renal insufficiency. His medications included atenolol, oxycodone, and OxyContin.

The patient was rolled over from study INS-05-001 and entered the maintenance period on (b) (6) using a FSS dose of 1200 mcg. On (b) (6) the patient died of cardiac arrhythmia.

The patient's death is unlikely related to study drug as he had tolerated the drug throughout study INS-05-001 and there was no change in the dose reported.

Patient 408004 was a 32 year-old Asian male with a history of lung cancer with brain and liver metastases. He had radiation therapy and chemotherapy. His medications included morphine, lactulose, and gefitinib.

This patient entered study INS-06-007 de novo. His initial FSS dose was 100 mcg. The patient entered the maintenance period the following day at a FSS dose of 100 mcg. The patient developed diarrhea on study day 24. The following day the patient experienced BTCP for which he took 100 mcg of fentanyl, suddenly vomited and collapsed, and died approximately 90 minutes after the last fentanyl dose. An autopsy was not performed and a death certificate was not available.

This patient reportedly died 90 minutes following use of study drug. The pharmacokinetic characteristics of fentanyl administered as FSS suggests that, at the time of death, fentanyl levels were past the maximum concentration and effect. Although the contribution of study drug to patient death cannot be excluded, there was no apparent relation to direct use of study drug. It appears this patient died as a result of a catastrophic event related to his underlying malignancy.

Patient 411002 was a 43-year-old Asian female with stomach cancer associated with dysphagia, anorexia, and ascites. Her medications included fentanyl patch, lactulose, acetaminophen, and codeine phosphate.

This patient was enrolled in study INS-06-007 de novo. Her initial FSS dose was 100 mcg. The patient entered the maintenance period the following one day at a FSS dose of 100 mcg. The patient died 14 days after initiating treatment with study drug, and her last FSS dose was two hours prior to her death.

There are too few details to determine whether study drug contributed to the patient's death. However, the pharmacokinetic characteristics of fentanyl delivered as FSS suggests that, at the time of death, fentanyl levels were past the maximum concentration and the peak effect making it less likely that the death was a direct effect of use of study drug.

7.3.2 Nonfatal Serious Adverse Events

There were a total of 59/359 (16%) patients who experienced SAEs that did not result in death during the development program, all during the multiple dose studies in cancer patients; 13 (4%) patients experienced SAEs during study INS-05-001 and 46 (13%) patients experienced SAEs during study INS-06-007. These SAEs were assessed by reviewing the CRFs, narratives, and datasets provided by the Applicant. Most SAEs were classified as neoplasms benign, malignant and unspecified, gastrointestinal disorders, or infections and infestations. The majority of SAEs were reported as due to the patients underlying malignancies, progression, and complications of underlying malignancy. As adjudicated by this review, none of the SAEs could definitely be

attributed to FSS use. All the events were found to be consistent with the patients' malignancies, treatments, concomitant medications, or other events surrounding the SAEs. The larger number of SAEs recorded during the maintenance period compared with the titration period of study INS-06-007 is an expected finding given that, over time, progression of the underlying malignancies and complications of underlying malignancy in the study patient population is part of their clinical course. Due to the large number of SAEs, this review does not contain a narrative summary for each patient who experienced an SAE. Instead, a tabular summary of all SAEs by study is provided below as well as a tabular summary of SAEs for each study period (open-label, double-blind, titration, maintenance) and dose (multiple-dose, 100 to 1600 mcg).

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There were a total of 13/130 (10%) patients recorded having SAE during this study; 7 patients during the open-label period and 6 patients during the double-blind period. In both the open-label and double-blind periods, all SAE were assessed to be unrelated to study drug.

Table 35 summarizes the incidence of SAE by preferred term for the open-label period and for the double-blind period.

Table 35: SAEs during open-label and double-blind periods

Preferred Term	Titration Period (N=130) n (%)	Double-Blind Period (N=98) n (%)
Any SAE	7 (5.4)	6 (6.1)
Abdominal Pain	1 (0.8)	1 (1.0)
Cellulitis	1 (0.8)	1 (1.0)
Fistula	1 (0.8)	—
Gastroenteritis Viral	—	1 (1.0)
Hyponatraemia	1 (0.8)	—
Leukopenia	1 (0.8)	—
Lung Cancer Metastatic	1 (0.8)	—
Malignant Neoplasm Progression	1 (0.8)	1 (1.0)
Metastases To Bone	1 (0.8)	—
Nausea	1 (0.8)	1 (1.0)
Paraplegia	—	1 (1.0)
Spinal Cord Neoplasm	1 (0.8)	—
Tachycardia	—	1 (1.0)
Vomiting	1 (0.8)	1 (1.0)

Source: Table 14.3.12 and 14.3.13
Source: INS-05-001 body FINAL STUDY REPORT, page 97/397 of the pdf

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There were a total of 46/359 (13%) patients recorded as having SAEs during this study; 14/229 (6%) patients during the titration period and 32/269 (12%) patients during the maintenance period. There were three patients whose SAEs were judged by the Investigator to be possibly related to study drug. Patient 119006 was on 800 mcg of FSS and had moderately elevated hepatic transaminases, and was discontinued from the study (see narrative in section 7.3.3 Dropouts and/or Discontinuations). Patient 142013 was on 1200 mcg of FSS and had a cardiac arrest (see narrative in section 7.3.1 Deaths). Patient 402006 was on 200 mcg of FSS and had moderate fatigue and diarrhea. The CRFs, data listings, and narratives were reviewed for each of these cases. There was insufficient information to determine whether the cause of SAE was related to study drug in any of the cases.

Table 36 summarizes the incidence of SAEs (other than death) for the titration and maintenance periods. Table 37 and Table 38 summarize the incidence of SAEs by multiple-dose during the titration and the maintenance period, respectively. The most

common SAE during the titration and maintenance periods appears to be related to patients' underlying progression of disease or complications of the underlying disease.

Table 36: Incidence of SAEs during titration and maintenance periods

Preferred Term	Titration Period (N=229) n (%)	Maintenance Period (N=269 n (%)
Malignant Neoplasm Progression	5 (2.2%)	60 (22.3%)
Disease Progression	2 (0.9%)	5 (1.9%)
Anaemia	NA	4 (1.5%)
Pneumonia	NA	4 (1.5%)
Cancer Pain	NA	4 (1.5%)
Nausea	1 (0.4%)	3 (1.1%)
Neutropenic Colitis	NA	3 (1.1%)
Vomiting	2 (0.9%)	3 (1.1%)
Non-Small Cell Lung Cancer	2 (0.9%)	3 (1.1%)
Prostate Cancer	1 (0.4%)	3 (1.1%)
Dyspnoea	NA	3 (1.1%)
Cellulitis	NA	3 (1.1%)
Pulmonary Embolism	1 (0.4%)	3 (1.1%)
Thrombocytopenia	NA	2 (0.7%)
Abdominal Pain	1 (0.4%)	2 (0.7%)
Fatigue	NA	2 (0.7%)
Oedema Peripheral	NA	2 (0.7%)
Diarrhoea	NA	2 (0.7%)
Gastritis	NA	2 (0.7%)
Electrolyte Imbalance	NA	2 (0.7%)
Deep Vein Thrombosis	NA	2 (0.7%)

NA=Not applicable; SAEs of this preferred term did not occur during this period

Sources: Section 14, Table 14.3.2.1A and Table 14.3.2.1B

Source: INS-06-007 body FINAL STUDY REPORT, page 115/808 of the pdf.

Table 37: Incidence of SAEs by multiple-dose during titration period

SYSTEM ORGAN CLASS/ PREFERRED TERM	100 N=88	200 N=43	400 N=26	600 N=16	800 N=20	1200 N=18	1600 N=18	TOTAL N=229
CARDIAC DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
GASTROINTESTINAL DISORDERS	3 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
ABDOMINAL PAIN	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
ASCITES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NAUSEA	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PANCREATITIS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VOMITING	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
DISEASE PROGRESSION	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
INFECTIONS AND INFESTATIONS	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)	4 (1.7%)
BACTERIAL SEPSIS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BREAST INFECTION	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
LIVER ABSCESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (0.4%)
SEPSIS SYNDROME	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.1%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
POST PROCEDURAL COMPLICATION	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
UROSTOMY COMPLICATION	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BACK PAIN	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	9 (10.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	10 (4.4%)
LUNG CANCER METASTATIC	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MALIGNANT ASCITES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (0.4%)
MALIGNANT NEOPLASM PROGRESSION	5 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.2%)
MYELODYSPLASTIC SYNDROME	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NON-SMALL CELL LUNG CANCER	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
PROSTATE CANCER	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NERVOUS SYSTEM DISORDERS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
HAEMORRHAGE INTRACRANIAL	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RENAL AND URINARY DISORDERS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	2 (0.9%)
HYDRONEPHROSIS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RENAL FAILURE CHRONIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.3%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
PNEUMONIA ASPIRATION	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PULMONARY EMBOLISM	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RESPIRATORY DISTRESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SUBJECTS WITH >=1 SAE OTHER THEN DEATH:	8 (9.1%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (5.0%)	2 (11.1%)	2 (11.1%)	14 (6.1%)
SUBJECTS WHO DIED	10 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (4.4%)

All percentages were based on the number of patients in the population and treatment group, and a patient was counted only once within each category.
Source: INS-06-007 body FINAL STUDY REPORT, page 598-599/808 of the pdf.

Table 38: Incidence of SAEs by multiple-dose during maintenance period

SYSTEM ORGAN CLASS/ PREFERRED TERM	100 N=42	200 N=45	400 N=42	600 N=29	800 N=34	1200 N=42	1600 N=35	TOTAL N=269
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (4.8%)	0 (0.0%)	1 (2.4%)	1 (3.4%)	0 (0.0%)	2 (4.8%)	1 (2.9%)	7 (2.6%)
ANAEMIA	2 (4.8%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	4 (1.5%)
NEUTROPENIA	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PANCYTOPENIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
THROMBOCYTOPENIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (2.9%)	2 (0.7%)
CARDIAC DISORDERS	0 (0.0%)	3 (6.7%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	5 (1.9%)
ARRHYTHMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
ATRIAL FIBRILLATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CARDIAC FAILURE	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CARDIO-RESPIRATORY ARREST	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CARDIOPULMONARY FAILURE	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
PYLORIC STENOSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
GASTROINTESTINAL DISORDERS	4 (9.5%)	4 (8.9%)	1 (2.4%)	2 (6.9%)	2 (5.9%)	1 (2.4%)	1 (2.9%)	15 (5.6%)
ABDOMINAL DISTENSION	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
ABDOMINAL PAIN	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
DIARRHOEA	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	2 (0.7%)
DYSPHAGIA	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GASTRITIS	1 (2.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
GASTROINTESTINAL FISTULA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GASTROINTESTINAL HAEMORRHAGE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GLOSSITIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NAUSEA	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	3 (1.1%)
NEUTROPENIC COLITIS	1 (2.4%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (1.1%)
STOMATITIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VOMITING	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	3 (1.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.4%)	3 (6.7%)	1 (2.4%)	0 (0.0%)	1 (2.9%)	5 (11.9%)	2 (5.7%)	13 (4.8%)
ASTHENIA	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DISEASE PROGRESSION	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (9.5%)	0 (0.0%)	5 (1.9%)
DRUG WITHDRAWAL SYNDROME	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
FATIGUE	0 (0.0%)	1 (2.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
OEDEMA PERIPHERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	2 (0.7%)
PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
PYREXIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
INFECTIONS AND INFESTATIONS	2 (4.8%)	2 (4.4%)	2 (4.8%)	0 (0.0%)	1 (2.9%)	3 (7.1%)	4 (11.4%)	14 (5.2%)
ABSCESS	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BACTERAEMIA	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CATHETER RELATED INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
CELLULITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)	3 (1.1%)
LOBAR PNEUMONIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
LOWER RESPIRATORY TRACT INFECTION	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
OESOPHAGEAL CANDIDIASIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PNEUMONIA	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	2 (4.8%)	1 (2.9%)	4 (1.5%)
SEPSIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SEPSIS SYNDROME	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SEPTIC SHOCK	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
STREPTOCOCCAL BACTERAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
URINARY TRACT INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.4%)	2 (4.4%)	0 (0.0%)	1 (3.4%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	6 (2.2%)
FEMORAL NECK FRACTURE	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
FIBULA FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
HIP FRACTURE	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

HUMERUS FRACTURE	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
OPEN WOUND	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
WOUND	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
INVESTIGATIONS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
HEPATIC ENZYME INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
INTERNATIONAL NORMALISED RATIO DECREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
METABOLISM AND NUTRITION DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	3 (1.1%)
DEHYDRATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
ELECTROLYTE IMBALANCE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
HYPOGLYCAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	2 (0.7%)
BACK PAIN	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MUSCULOSKELETAL PAIN	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MYOSITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	22 (52.4%)	13 (28.9%)	8 (19.0%)	11 (37.9%)	11 (32.4%)	5 (11.9%)	7 (20.0%)	77 (28.6%)
BLADDER CANCER	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BREAST CANCER METASTATIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
CANCER PAIN	1 (2.4%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	4 (1.5%)
COLON CANCER METASTATIC	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
LARYNGEAL CANCER	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
LIP AND/OR ORAL CAVITY CANCER	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
LUNG NEOPLASM MALIGNANT	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MALIGNANT NEOPLASM PROGRESSION	18 (42.9%)	10 (22.2%)	7 (16.7%)	7 (24.1%)	9 (26.5%)	4 (9.5%)	5 (14.3%)	60 (22.3%)
METASTASES TO BONE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
METASTASES TO SPINE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
MULTIPLE MYELOMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NON-SMALL CELL LUNG CANCER	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	3 (1.1%)
PROSTATE CANCER	0 (0.0%)	1 (2.2%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.1%)
NERVOUS SYSTEM DISORDERS	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CEREBROVASCULAR ACCIDENT	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RENAL AND URINARY DISORDERS	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RENAL FAILURE ACUTE	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (2.4%)	2 (4.4%)	1 (2.4%)	2 (6.9%)	2 (5.9%)	2 (4.8%)	1 (2.9%)	11 (4.1%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DYSPNOEA	1 (2.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	3 (1.1%)
EMPHYSEMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
PLEURAL EFFUSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
PNEUMONIA ASPIRATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PULMONARY EMBOLISM	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (3.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (1.1%)
RESPIRATORY DISTRESS	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BLISTER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VASCULAR DISORDERS	1 (2.4%)	0 (0.0%)	1 (2.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.1%)
DEEP VEIN THROMBOSIS	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
ORTHOSTATIC HYPOTENSION	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SUBJECTS WITH >=1 SAE OTHER THEN DEATH:	4 (9.5%)	4 (8.9%)	2 (4.8%)	4 (13.8%)	4 (11.8%)	7 (16.7%)	7 (20.0%)	32 (11.9%)
SUBJECTS WHO DIED	21 (50.0%)	17 (37.8%)	8 (19.0%)	9 (31.0%)	12 (35.3%)	7 (16.7%)	5 (14.3%)	79 (29.4%)

All percentages were based on the number of patients in the population and treatment group, and a patient was counted only once within each category.
Source: INS-06-007 body FINAL STUDY REPORT, page 600-604/808 of the pdf.

7.3.3 Dropouts and/or Discontinuations

A total of 67/359 (19%) patients from studies INS-05-001 and INS-06-007 discontinued study medication due to AEs; 9/359 (3%) patients discontinued study medication during study INS-05-001 and 58/359 (16%) patients discontinued study medication during study INS-06-007. These AEs and their association to study drug were assessed by reviewing the CRFs, narratives, and datasets provided by the Applicant.

INS-05-001

The Applicant indicated there were a total of 7 (2%) patients who discontinued from this study due to AEs; 6 patients discontinued during the open-label period and 1 patient discontinued during the double-blind period. The Applicant also indicated there were 16 patients in the category of patient's decision to withdraw from the study and two patients in the category of investigator's decision. These categories were non-descriptive and uninformative. A review of the source material showed patients who discontinued from the study because of "patient decision" and "investigator decision" was for reasons that included adverse events. My review of the CRFs, narratives, and datasets allowed me to adjudicate there were a total of 9 (3%) patients who discontinued from the study because of AEs associated with study drug. All discontinuations were recorded during the open-label period. There was one patient who was recorded to have been withdrawn from the study because of SAE during the double-blind period. However, the details of this case suggest this patient should have been categorized as "intercurrent illness, AE or surgery" rather than AEs/SAE. Narratives for these 9 patients are provided below. The AEs that lead to discontinuation from this study included somnolence (3), nausea (2), anorexia, diarrhea, chest tightness, mood swings, irritation at drug application site, confusion, disorientation, paranoia, vomiting, felt overmedicated, dizziness, difficulty concentrating, and progression of malignancy. There was insufficient information to determine the AEs leading to discontinuation of study drug were definitively related to study drug in any of the cases. The AEs leading to discontinuation of study drug may have been related to the patient's underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs.

Patient 105001 experienced anorexia on Study Day 1 of the open-label period. The anorexia was judged by the Investigator to be moderate and probably related to study drug. The study drug was discontinued 13 days following the initial FSS dose. Anorexia resolved without intervention.

Patient 112008 experienced nausea and diarrhea on Study Day 1 of the open-label period. The nausea and diarrhea were judged by the Investigator to be moderate and probably related to study drug. The study drug was discontinued the same day. The AEs resolved without intervention.

Patient 124008 experienced chest tightness and mood swings on Study Day 3 of the open-label period. The chest tightness and mood swings were judged by the Investigator to be mild and possibly related to study drug, and the study drug was discontinued. The AEs resolved without intervention.

Patient 127009 experienced irritation at the study drug application site on Study Day 9 of the open-label period. The irritation was judged by the Investigator to be severe and probably related to study drug. On Study Day 10, the patient experienced irritation at the

study drug application site application that was judged by the Investigator to be moderate and probably related to study drug. In addition, the patient experienced oral pain, which was judged by the Investigator to be severe and probably related to study drug. The study drug was discontinued on the same day; 10 days following her initial FSS dose. The AEs resolved without intervention.

Patient 135001 experienced confusion state, disorientation and somnolence on Study Day 1 of the open-label period. The confusion, disorientation and somnolence were judged by the Investigator to be mild and possibly related to study drug, and study drug was discontinued. The patient's concomitant medications included prednisone, Zoloft, Darvocet, fentanyl patch, Neurontin, oxycodone, OxyContin, Compazine, phenergran, and morphine. The AEs resolved without intervention.

Subject 143001 experienced paranoia and somnolence on Study Day 3 of the open-label period. The paranoia and somnolence were judged by the Investigator to be mild and possibly related to study drug. The study drug was discontinued four days following the initial FSS dose. The AEs resolved without intervention.

Patient 111002 was recorded to have discontinued from the study because of patient decision. Review of the source materials indicate this patient withdrew from the study because of nausea and vomiting associated with the study drug.

It appeared that this patient withdrew from the study because of AEs.

Patient 140002 was recorded to have discontinued from the study because of patient decision. Review of the source materials indicate this patient withdrew from the study because patient felt overmedicated from the study drug and the underlying grade 1 mucositis on sides of mouth and tongue has not resolved. The patient's concomitant medications included Cymbalta, Neurontin, carvedilol, meclizine, Duragesic patch, Dilaudid, Lidoderm patch, Percocet, and pregabalin.

It appeared that this patient withdrew from the study because of AEs.

Patient 142002 was recorded to have discontinued from the study because of investigator decision. Review of the source materials indicate this patient withdrew from the study because patient had nausea, somnolence, dizziness, and difficulty concentrating associated with the study drug.

It appeared that this patient withdrew from the study because of AEs.

Patient 119005 was recorded to have discontinued from the study because of AEs/SAE. Review of the source materials indicate this patient was hospitalized for progression of the underlying cervical cancer, was admitted to hospice care, and died. It

would seem this patient should have been categorized as “intercurrent illness, AE or surgery” rather than AEs/SAE. See section 7.3.1 Deaths.

INS-06-007

The Applicant indicated there were a total of 58/359 (16%) patients who discontinued from this study due to AEs; 17/229 (7%) patients discontinued during the titration period and 41/269 (15%) patients discontinued during the maintenance period. The larger number of AEs leading to discontinuation from this study recorded during the maintenance period compared with the titration period is an expected finding given that, over time, progression of the underlying malignancies and complications of underlying malignancy in the study patient population is part of their clinical course. No obvious associations with dose or study period were noted. The most common AEs by system organ class leading to study drug discontinuation during the titration period was neuropsychiatric disorders (3.5%), which was followed by gastrointestinal disorders (2.6%) and neoplasms, benign, malignant and unspecified (2.2%). The most common AEs by system organ class leading to study drug discontinuation during the maintenance period was neoplasms, benign, malignant and unspecified (9.3%), which was followed by gastrointestinal disorders (2.2%), neuropsychiatric disorders (1.5%) and infections and infestations (1.5%). Table 39 summarizes the AEs leading to study drug discontinuation during the titration period by system organ class and preferred term. Table 40 summarizes the AEs leading to study drug discontinuation during the maintenance period by system organ class and preferred term.

Table 39: Incidence of AEs leading to study drug discontinuation – titration period

SYSTEM ORGAN CLASS/ PREFERRED TERM	100 N=88	200 N=43	400 N=26	600 N=16	800 N=20	1200 N=18	1600 N=18	TOTAL N=229
ANY AE LEADING TO STUDY DRUG DISCONTINUATION (TOTAL)	16 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	17 (7.4%)
EYE DISORDERS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VISUAL DISTURBANCE	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GASTROINTESTINAL DISORDERS	6 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (2.6%)
CONSTIPATION	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DIARRHOEA	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
FLATULENCE	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NAUSEA	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
STOMATITIS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
VOMITING	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
APPLICATION SITE IRRITATION	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
FEELING DRUNK	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
OEDEMA PERIPHERAL	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
CANCER PAIN	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MALIGNANT NEOPLASM PROGRESSION	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MYELODYSPLASTIC SYNDROME	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NON-SMALL CELL LUNG CANCER	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PROSTATE CANCER	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NERVOUS SYSTEM DISORDERS	4 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	5 (2.2%)
AMNESIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
DIZZINESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

HEADACHE	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
SOMNOLENCE	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
PSYCHIATRIC DISORDERS	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	3 (1.3%)
CONFUSIONAL STATE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.4%)
DEPRESSION	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
PANIC ATTACK	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DYSPNOEA	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RESPIRATORY DISTRESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

Percents are based on number of patients in the population and treated group (N) and a patient is counted once within each category.
Source: INS-06-007 body FINAL STUDY REPORT, page 587-588/808 of the pdf.

Table 40: Incidence of AEs leading to study drug discontinuation – maintenance period

SYSTEM ORGAN CLASS/ PREFERRED TERM	100 N=42	200 N=45	400 N=42	600 N=29	800 N=34	1200 N=42	1600 N=35	TOTAL N=269
ANY AE LEADING TO STUDY DRUG DISCONTINUATION (TOTAL)	9 (21.4%)	3 (6.7%)	5 (11.9%)	6 (20.7%)	7 (20.6%)	8 (19.0%)	3 (8.6%)	41 (15.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
ANAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
THROMBOCYTHAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
GASTROINTESTINAL DISORDERS	3 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	2 (4.8%)	0 (0.0%)	6 (2.2%)
ABDOMINAL DISTENSION	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CHEILITIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CONSTIPATION	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DIARRHOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
HAEMATEMESIS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.4%)	0 (0.0%)	2 (0.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	1 (2.9%)	4 (1.5%)
ASTHENIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
DISEASE PROGRESSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	0 (0.0%)	3 (1.1%)
INFECTIONS AND INFESTATIONS	0 (0.0%)	1 (2.2%)	1 (2.4%)	1 (3.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	4 (1.5%)
ABSCESS	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PNEUMONIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
SEPTIC SHOCK	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
TOOTH INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
TONGUE INJURY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)

INVESTIGATIONS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
HEPATIC ENZYME INCREASED	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
PHYSICAL EXAMINATION ABNORMAL	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
METABOLISM AND NUTRITION DISORDERS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	2 (0.7%)
ANOREXIA	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
HYPOKALAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
HYPONATRAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6 (14.3%)	2 (4.4%)	5 (11.9%)	4 (13.8%)	6 (17.6%)	1 (2.4%)	1 (2.9%)	25 (9.3%)
BLADDER CANCER	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
CANCER PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
COLON CANCER METASTATIC	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
MALIGNANT NEOPLASM PROGRESSION	5 (11.9%)	2 (4.4%)	4 (9.5%)	3 (10.3%)	5 (14.7%)	1 (2.4%)	1 (2.9%)	21 (7.8%)
NON-SMALL CELL LUNG CANCER	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
NERVOUS SYSTEM DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
DEPRESSED LEVEL OF CONSCIOUSNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
PSYCHIATRIC DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	3 (1.1%)
CONFUSIONAL STATE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
EUPHORIC MOOD	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	2 (0.7%)
RENAL AND URINARY DISORDERS	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
DYSURIA	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (2.9%)	2 (0.7%)
ACUTE RESPIRATORY DISTRESS SYNDROME	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
DYSPNOEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.8%)	0 (0.0%)	2 (0.7%)
DECUBITUS ULCER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)
RASH PAPULAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.4%)

Percents are based on number of patients in the population and treated group (N) and a patient is counted once within each category.
Source: INS-06-007 body FINAL STUDY REPORT, page 589-591/808 of the pdf.

There were 18 patients with AEs that were assessed by the Investigator to be possibly or probably related to study drug leading to discontinuation of study drug. The AEs leading to discontinuation of study drug were euphoria, constipation, elevated liver enzymes, headache, nausea and dizziness, vomiting, sleepiness, cardiac arrhythmia, “high” (euphoric) feeling, feeling drunk, nausea, burning under tongue and entire mouth, confusion and amnesia, burning under tongue, flatulence and diarrhea, stomatitis and visual disturbance. The CRFs, narratives, and data listings were reviewed for each of these patients. There was insufficient information to determine the AEs leading to discontinuation of study drug were related to study drug in any of the cases, except possibly patient 231005 (see narrative below).

Patient 231005 was a 69 year-old white male with a history of squamous cell carcinoma of the head and neck and poorly differentiated non-small cell lung carcinoma, and has had cancer related surgery, radiotherapy, and chemotherapy. Other significant medical history included radiation induced cough and hoarseness, COPD, easy bruisability and bleeding, anorexia, memory problems, dysgeusia, peripheral neuropathy, impaired balance, muscular deterioration, cardiac dysrhythmias, ischemic heart disease, and prolonged QT interval. His medications included fentanyl patch, acetaminophen, Ambien, Dilaudid, lorazepam, methadone, and Zofran.

This patient entered study INS-06-007 de novo. His initial FSS dose was 100 mcg. The next day the patient reported burning under his tongue and throughout his entire mouth for 3-5 minutes following FSS use. These symptoms were reported to recur with

subsequent FSS use. The study drug was discontinued four days following initial FSS dosing.

Given the AEs occurring within minutes of study drug administration and recurrence of AEs following subsequent study drug administration, it may be possible that the study drug could have contributed to this patient's AEs.

The Applicant indicated there were a total of 40 patients in the category of patient's decision to withdraw from the study; 19 during the titration period and 21 during the maintenance period. This category was non-descriptive and uninformative. A review of the CRFs, narratives, and datasets provided by the Applicant showed patients who discontinued from the study because of "patient decision" was for reasons that included adverse events. Two of these patients (143002 and 233002) were recorded to have discontinued from this study because of adverse events (see narratives below), one patient (307001) decided to discontinue from the study because of "sore mouth with increasing dose; minimal pain relief with advancing disease" (see Section 7.3.5 Adverse events involving the mouth), 13 patients discontinued from this studies for reasons other than adverse events, and no detail information was available for 24 patients in this category. This suggests at least one of the 40 patients who discontinued from the study in the category of patient's decision was because of adverse events, and more patients in this category may have discontinued because of adverse events.

Patient 143002 was a 47 year-old white female with a history of metastatic breast cancer to the spine, and has had radiation therapy and chemotherapy. Other significant medical history included pulmonary embolism, acid reflux, night sweats and hot flashes, chronic constipation, tingling in hands and feet secondary to chemotherapy, sinusitis, and frequent nosebleeds. Her medications included Effexor, gabapentin, lorazepam, OxyContin, and Zometa.

This patient entered study INS-06-007 de novo. Her initial FSS dose of 100 mcg was titrated up to 600 mcg over 20 days. During the titration period, the patient reported a variety of mild self-limited symptoms that included altered taste in foods, hallucinations, a white coating on her tongue, and hypertension. However, the patient continued with a 600 mcg dose of FSS. The patient reported experiencing a moderate "high" (preferred term: euphoric) feeling 46 days into her maintenance period, which continued for the next 10 days. The Investigator judged this "high" to be probably related to study drug, and the study drug was discontinued on the 56th day of the maintenance period; 10 days from the onset of the patient's "high." The patient's euphoria may have been related to study drug.

Patient 233002 was a 39 year-old white female with a history of stage I soft tissue sarcoma of the left lower extremity, lung and the lymphatic, and has had radiotherapy and chemotherapy. Other significant medical history included constipation, dyspnea, difficulty sleeping, anxiety, nausea and vomiting, urinary retention, weakness,

myofascial pain, urinary frequency, migraine, depression, edema, herpes, air hunger, and agitation; allergies to Vicodin, Stadol, and Compazine. Her medications included acetaminophen, albuterol, Ativan, Benadryl, benzonatate, haloperidol, hyocyamine, lorazepam, Dilaudid, ibuprofen, lactulose, Lasix, morphine, nortriptyline, Nystatin, Phenergan, Reglan, and temazepam.

This patient entered study INS-06-007 de novo. Her initial FSS dose of 100 mcg was titrated to 200 mcg over four days. The patient reported increased constipation of mild intensity four days following her first dose of FSS. The Investigator judged the increased constipation to be possibly related to study drug, and the study drug was discontinued The constipation resolved four days after achieving the 200 mcg dose; seven days following the patient's first dose of FSS. The constipation may have been related to study drug.

7.3.4 Significant Adverse Events

Significant opioid-related adverse events that led to discontinuation from the clinical trials include nausea, vomiting, constipation, euphoria, dizziness, headache, disorientation, sedation, and irritation of the oral cavity. Except for irritation of the oral cavity, these events would be expected in this study population, either because of background opioid medications or the study drug.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events involving the mouth

Oral tolerability and the presence of an abnormal oral cavity associated with FSS use were assessed in the multiple-dose Phase 3 studies at scheduled visits. Patients oral cavities were examined for abnormalities such as infection, mucositis, cold sores, viral lesions, local irritation, periodontal disease, piercings.

INS-05-001

Oral cavity AEs were recorded in 5/130 (4%) patients during the open-label period. The AEs, included sublingual erythema, edema, inflammation, difficulty swallowing, difficulty eating, application site irritation or stomatitis. One patient (127009) was identified who discontinued from the study during the open-label period because oral cavity AEs; see narrative in section 7.3.3 INS-05-001. There were no oral cavity adverse events recorded during the double-blind period.

INS-06-007

During the titration period, most of the patients examined had no evidence of infection, mucositis, cold sores, viral lesions, local irritation, periodontal disease, piercings, and only periodontal disease was detected in 5 patients (2%). There was no change in these findings from screening to the titration visit and during the maintenance period. There were 7 patients with mucositis at the time of entry into the study, and continued to have mucositis during the study. Four patients were identified who discontinued from the study because of AEs related to their oral cavity.

Patient 231005: See section 7.3.3 study INS-06-007.

Patient 233021 was a 49 year-old white female with a history of stage IV metastatic adenocarcinoma of the colon, and has had right hemicolectomy with synchronous liver wedge resection, left extended hepatectomy, and chemotherapy. Other significant medical history included migraine headaches, nausea, chronic anxiety, panic attacks, depression, sore throat, severe peripheral neuropathy, mouth pain, hypoxia, gastroesophageal reflux, anemia, thrombocytopenia, diarrhea, constipation, nephrolithiasis, fatty/enlarged liver, neutropenia, fatigue, weakness, and mucositis; allergies to Lyrica and Dilaudid. Her medications included albuterol, Benadryl, Klonopin, OxyContin, Phenergan, Remeron, Roxicodone, Spiriva, and Zoloft.

This patient entered study INS-06-007 de novo at a starting dose of 100 mcg of FSS. She reported self-limited mild burning under her tongue following the initial FSS dose. The Investigator judged the burning sensation to be probably related to study drug, and the study drug was discontinued.

There was insufficient information from the CRF, narrative, and data listing to determine the AEs leading to discontinuation from the study drug were definitively related to study drug. The AEs leading to discontinuation of study drug may have been related to the patient's underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs.

Patient 413002 was a 73 year-old Asian female with a history of stage IV non-Hodgkin's lymphoma. Other significant medical history included constipation, lumbar spondylitis, and scoliosis. Her medications included diclofenac, morphine, and Ultracet.

This patient entered study INS-06-007 de novo. Her initial FSS dose was 100 mcg. Two days after the patient's initial FSS dose, the patient complaint of mild stomatitis and dimness of vision. The Investigator judged the symptoms to be possibly related to study drug, and the study drug was reported to have been discontinued the day after the initial FSS dosing; one day prior to onset of patient's symptoms. The stomatitis and dimness of vision resolved 11 days after discontinuation of study drug.

Given that stomatitis and dimness of vision occurred one day after the study drug was discontinued, it was unclear that these AEs were related to study drug. There was

insufficient information from CRF, narrative, and data listing to determine the AEs leading to discontinuation from study drug were definitively related to study drug. The AEs leading to discontinuation of study drug may have been related to the patient's underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs.

Patient 307001 was a 49 year-old female with metastatic lung cancer to the liver. Her medications included fentanyl patch, hydromorphone, lorazepam, amitriptyline, dexamethasone, levothyroxine, vitamins, fish oil, lycopene, and herbal remedies.

This patient entered study INS-06-007 de novo on 09 September 2008. At the time of enrollment there was no oral lesions/infections recorded. Her initial FSS dose was 100 mcg. She reached a stable dose of 1200 mcg three days later and entered the maintenance period. It was recorded that she had active infection in her mouth and she had a sore tongue; mucositis, cold sores, viral lesions, local irritation, and periodontal disease were not present. The patient discontinued from the study because of "sore mouth" and "burning under tongue at drug application site after dosing." The patient's last FSS dose was 23 September 2008, 14 days following her initial FSS dose.

It would appear this patient developed oral infection and sore tongue three days into the study at a time when she achieved a stable FSS dose. It also appeared the patient was on FSS treatment for two weeks before she withdrew from the study. The unclear part was when the patient first complaint of "sore mouth" and "burning under tongue…" (i.e., before or after development of oral infection and sore tongue). It was possible that the patient experienced worsening of her oral infection, which contributed to her decision to withdraw from the study. There was insufficient information from the CRF, narrative, and data listing to determine the AEs leading to discontinuation from the study drug were definitively related to study drug. The AEs leading to discontinuation of study drug may have been related to the patient's underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly observed adverse reactions among the 359 opioid-tolerant cancer patients treated with FSS in the multiple-dose Phase 3 studies included nausea, somnolence, dizziness, vomiting, constipation, and headache. As the Phase 3 clinical trials were designed to evaluate safety and efficacy in opioid tolerant patients with cancer breakthrough pain, the use of concomitant opioids makes it difficult to determine whether opioid-related AEs were due to FSS or the other opioid used by the patient.

INS-05-001

A summary of AEs by system organ class and preferred term are provided for the open-label, dose-titration period in Table 41. There were a total of 78 (60%) patients who reported at least one AE. The most frequently reported system organ class adverse event was gastrointestinal disorders, and this was reported by approximately 28% of patients. System organ class adverse events reported in ≥10% of patients included gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, and infections and infestations, and respiratory, thoracic and mediastinal disorders.

Table 41: Incidence of adverse events – open-label, dose-titration period

	Total (N=130)	
Any Adverse Events	78	(60.0%)
Gastrointestinal Disorders	36	(27.7%)
Nausea	17	(13.1%)
Vomiting	10	(7.7%)
Diarrhoea	7	(5.4%)
Constipation	5	(3.8%)
Stomatitis	5	(3.8%)
Dry Mouth	2	(1.5%)
Abdominal Discomfort	1	(0.8%)
Abdominal Distension	1	(0.8%)
Abdominal Pain	1	(0.8%)
Abdominal Pain Upper	1	(0.8%)
Dysphagia	1	(0.8%)
Flatulence	1	(0.8%)
Gastric Ulcer	1	(0.8%)
Gastrointestinal Motility Disorder	1	(0.8%)
Gingival Hyperplasia	1	(0.8%)
Glossitis	1	(0.8%)
Hyperchlorhydria	1	(0.8%)
Hypoaesthesia Oral	1	(0.8%)
Odynophagia	1	(0.8%)
Oral Pain	1	(0.8%)
Retching	1	(0.8%)
Tongue Ulceration	1	(0.8%)
Nervous System Disorders	29	(22.3%)
Somnolence	11	(8.5%)
Dizziness	10	(7.7%)
Headache	5	(3.8%)
Sedation	4	(3.1%)
Dysgeusia	3	(2.3%)
Lethargy	2	(1.5%)
Areflexia	1	(0.8%)

Balance Disorder	1	(0.8%)
Burning Sensation	1	(0.8%)
Disturbance In Attention	1	(0.8%)
Dyskinesia	1	(0.8%)
Facial Palsy	1	(0.8%)
Hyperreflexia	1	(0.8%)
Hypoaesthesia	1	(0.8%)
Paraesthesia	1	(0.8%)
General Disorders And Administration Site Conditions	28	(21.5%)
Pyrexia	8	(6.2%)
Oedema Peripheral	7	(5.4%)
Asthenia	4	(3.1%)
Fatigue	4	(3.1%)
Application Site Irritation	3	(2.3%)
Adverse Drug Reaction	1	(0.8%)
Catheter Related Complication	1	(0.8%)
Catheter Site Erythema	1	(0.8%)
Chest Discomfort	1	(0.8%)
Feeling Abnormal	1	(0.8%)
Localised Oedema	1	(0.8%)
Mucosal Inflammation	1	(0.8%)
Pain	1	(0.8%)
Thirst	1	(0.8%)
Infections And Infestations	13	(10.0%)
Urinary Tract Infection	5	(3.8%)
Cellulitis	2	(1.5%)
Gastroenteritis Viral	1	(0.8%)
Oral Herpes	1	(0.8%)
Pneumonia	1	(0.8%)
Pyelonephritis	1	(0.8%)
Upper Respiratory Tract Infection	1	(0.8%)
Viral Infection	1	(0.8%)
Viral Upper Respiratory Tract Infection	1	(0.8%)
Respiratory, Thoracic And Mediastinal Disorders	13	(10.0%)
Dyspnoea	4	(3.1%)
Cough	3	(2.3%)
Increased Bronchial Secretion	3	(2.3%)
Dysphonia	1	(0.8%)
Epistaxis	1	(0.8%)
Hiccups	1	(0.8%)
Increased Upper Airway Secretion	1	(0.8%)
Pharyngolaryngeal Pain	1	(0.8%)
Pulmonary Congestion	1	(0.8%)
Respiratory Tract Congestion	1	(0.8%)
Throat Irritation	1	(0.8%)
Wheezing	1	(0.8%)
Psychiatric Disorders	10	(7.7%)
Confusional State	4	(3.1%)
Insomnia	4	(3.1%)
Agitation	2	(1.5%)
Hallucination	2	(1.5%)
Anxiety	1	(0.8%)
Depression	1	(0.8%)
Disorientation	1	(0.8%)
Mood Swings	1	(0.8%)
Paranoia	1	(0.8%)
Restlessness	1	(0.8%)
Skin And Subcutaneous Tissue Disorders	9	(6.9%)
Hyperhidrosis	2	(1.5%)
Alopecia	1	(0.8%)
Blister	1	(0.8%)
Erythema	1	(0.8%)

Pruritus	1	(0.8%)
Rash	1	(0.8%)
Rash Erythematous	1	(0.8%)
Rash Maculo-Papular	1	(0.8%)
Skin Lesion	1	(0.8%)
Urticaria	1	(0.8%)
Musculoskeletal And Connective Tissue Disorders	8	(6.2%)
Back Pain	3	(2.3%)
Arthralgia	2	(1.5%)
Fistula	2	(1.5%)
Joint Swelling	2	(1.5%)
Limb Discomfort	1	(0.8%)
Mobility Decreased	1	(0.8%)
Muscle Spasms	1	(0.8%)
Metabolism And Nutrition Disorders	7	(5.4%)
Anorexia	2	(1.5%)
Dehydration	2	(1.5%)
Decreased Appetite	1	(0.8%)
Hypokalaemia	1	(0.8%)
Hyponatraemia	1	(0.8%)
Increased Appetite	1	(0.8%)
Malnutrition	1	(0.8%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	5	(3.8%)
Malignant Neoplasm Progression	3	(2.3%)
Cancer Pain	1	(0.8%)
Lung Cancer Metastatic	1	(0.8%)
Metastases To Bone	1	(0.8%)
Spinal Cord Neoplasm	1	(0.8%)
Renal And Urinary Disorders	4	(3.1%)
Urinary Retention	3	(2.3%)
Bladder Distension	1	(0.8%)
Bladder Spasm	1	(0.8%)
Haematuria	1	(0.8%)
Micturition Urgency	1	(0.8%)
Vascular Disorders	4	(3.1%)
Deep Vein Thrombosis	1	(0.8%)
Hypertension	1	(0.8%)
Hypotension	1	(0.8%)
Venous Stasis	1	(0.8%)
Blood And Lymphatic System Disorders	3	(2.3%)
Anaemia	1	(0.8%)
Leukopenia	1	(0.8%)
Lymphadenopathy	1	(0.8%)
Injury, Poisoning And Procedural Complications	3	(2.3%)
Fall	2	(1.5%)
Contusion	1	(0.8%)
Device Breakage	1	(0.8%)
Excoriation	1	(0.8%)
Radiation Injury	1	(0.8%)
Investigations	3	(2.3%)
Blood Bilirubin Increased	1	(0.8%)
Blood Creatinine Increased	1	(0.8%)
Blood Glucose Increased	1	(0.8%)
Blood Potassium Decreased	1	(0.8%)
Blood Urea Increased	1	(0.8%)
International Normalised Ratio Increased	1	(0.8%)
Prothrombin Time Prolonged	1	(0.8%)
Reproductive System And Breast Disorders	3	(2.3%)
Amenorrhoea*	1	(1.4%)
Epididymitis*	1	(1.6%)
Vaginal Haemorrhage*	1	(1.4%)
Ear And Labyrinth Disorders	2	(1.5%)
Ear Pain	1	(0.8%)
Vertigo	1	(0.8%)
Cardiac Disorders	1	(0.8%)
Tachycardia	1	(0.8%)
Eye Disorders	1	(0.8%)
Dry Eye	1	(0.8%)
Hepatobiliary Disorders	1	(0.8%)
Jaundice Cholestatic	1	(0.8%)

*Gender-specific AEs: Percent based on number of patients in the specific gender.
Source: INS-05-001 Final study report, page 258-263/397 of pdf.

Table 42 shows adverse events by preferred term that occurred in >3% of the patients during the open-label, dose-titration period. The most frequently reported adverse event in these patients was nausea (13%). Adverse events occurring in >5% of these patients included nausea, somnolence, dizziness, vomiting, pyrexia, and diarrhea.

Table 42: Incidence of adverse events >3% of patients – open-label period, dose-titration period

Preferred Term	Total (N=130) n (%)
Nausea	17 (13.1%)
Somnolence	11 (8.5%)
Dizziness	10 (7.7%)
Vomiting	10 (7.7%)
Pyrexia	8 (6.2%)
Diarrhoea	7 (5.4%)
Oedema peripheral	7 (5.4%)
Constipation	5 (3.8%)
Headache	5 (3.8%)
Stomatitis	5 (3.8%)
Urinary tract infection	5 (3.8%)
Asthenia	4 (3.1%)
Confusional state	4 (3.1%)
Dyspnoea	4 (3.1%)
Fatigue	4 (3.1%)
Insomnia	4 (3.1%)
Sedation	4 (3.1%)

Source: INS-05-001 Final study report, page 90/397 of pdf.

A composite summary of AEs associated with study drug use and route of study drug administration by maintenance (successful) dose is provided for the open-label period in Table 43. There were 33 patients (25%) in the open-label period that experienced an adverse event associated with study drug use (e.g., sleepiness, dizziness, nausea,

vomiting, confusion, hallucinations, weakness, shortness of breath, slow breathing or hypoventilation, slow heart rate, low blood pressure, headache, itching, rash, abdominal pain, and cold sores). Most of the AEs were observed to occur with FSS dose ≥600 mcg. There were five patients (4%) in the titration period that experienced an adverse event associated with the mode of study drug administration (e.g., sublingual erythema, edema, inflammation, difficulty swallowing, difficulty eating, application site irritation, and stomatitis).

Table 43: Adverse events associated with FSS use and mode of administration – open-label period

	100 mcg (N=4)	200 mcg (N=7)	400 mcg (N=15)	600 mcg (N=15)	800 mcg (N=24)	1200 mcg (N=20)	1600 mcg (N=13)	No Succ. Dose (N=32)	Total (N=130)
Use*	1 (25.0%)	2 (28.6%)	0 (0.0%)	6 (40.0%)	6 (25.0%)	6 (30.0%)	4 (30.8%)	8 (25.0%)	33 (25.4%)
Mode**	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	3 (9.4%)	5 (3.8%)

* AEs associated with study medication use: The occurrence of at least one of sleepiness, somnolence, dizziness, nausea, vomiting, confusion, confusional state, disorientation, hallucinations, weakness, shortness of breath, dyspnoea, slow breathing, hypoventilation, slow heart rate, low blood pressure, headache, itching, rash, abdominal pain, or occurrence of cold sores.
** AEs associated with mode of administration: The occurrence of at least one of sublingual erythema, edema, inflammation, difficulty swallowing, difficulty eating, application site irritation, or stomatitis.
Note: Only AEs possibly related or probably related to study medication are reported in this table.
Source: INS-05-001 Final study report, page 288/397 of pdf.

A summary of AEs by system organ class and preferred term are provided for the double-blind placebo-controlled cross over period in Table 44. There were a total of 47 (48%) patients who reported at least one AE. The most frequently reported system organ class adverse event was gastrointestinal disorders, and this was reported in 17% of patients. System organ class adverse events reported in >10% of patients included gastrointestinal disorders, and general disorders and administration site conditions.

Table 44: Incidence of adverse events – double-blind placebo-controlled cross over period

	Total (N=98)	
Any Adverse Events	47	(48.0%)
Gastrointestinal Disorders	17	(17.3%)
Nausea	7	(7.1%)
Vomiting	4	(4.1%)
Diarrhoea	3	(3.1%)
Abdominal Pain Lower	2	(2.0%)
Dry Mouth	2	(2.0%)
Abdominal Pain	1	(1.0%)
Aphthous Stomatitis	1	(1.0%)
Ascites	1	(1.0%)
Colitis	1	(1.0%)
Flatulence	1	(1.0%)
Lip Disorder	1	(1.0%)
Oral Mucosal Discolouration	1	(1.0%)
Retching	1	(1.0%)
Salivary Gland Enlargement	1	(1.0%)
Stomatitis	1	(1.0%)
General Disorders And Administration Site Conditions	11	(11.2%)
Oedema Peripheral	5	(5.1%)
Asthenia	2	(2.0%)
Fatigue	2	(2.0%)
Chest Discomfort	1	(1.0%)
Chills	1	(1.0%)
Malaise	1	(1.0%)
Mass	1	(1.0%)
Pain	1	(1.0%)
Pyrexia	1	(1.0%)
Infections And Infestations	9	(9.2%)
Urinary Tract Infection	3	(3.1%)
Candidiasis	1	(1.0%)
Cellulitis	1	(1.0%)
Extradural Abscess	1	(1.0%)
Fungal Infection	1	(1.0%)
Gastroenteritis Viral	1	(1.0%)
Nasopharyngitis	1	(1.0%)
Oral Viral Infection	1	(1.0%)
Pharyngitis	1	(1.0%)
Pneumonia	1	(1.0%)
Sinusitis	1	(1.0%)
Nervous System Disorders	9	(9.2%)
Headache	3	(3.1%)
Dizziness	2	(2.0%)
Somnolence	2	(2.0%)
Neuralgia	1	(1.0%)
Paraplegia	1	(1.0%)
Spinal Cord Disorder	1	(1.0%)
Skin And Subcutaneous Tissue Disorders	9	(9.2%)
Hyperhidrosis	5	(5.1%)
Dermatitis Contact	1	(1.0%)
Ecchymosis	1	(1.0%)
Rash Macular	1	(1.0%)
Stasis Dermatitis	1	(1.0%)
Respiratory, Thoracic And Mediastinal Disorders	7	(7.1%)
Cough	3	(3.1%)
Epistaxis	1	(1.0%)
Pharyngeal Inflammation	1	(1.0%)
Productive Cough	1	(1.0%)
Wheezing	1	(1.0%)
Musculoskeletal And Connective Tissue Disorders	6	(6.1%)
Pain In Extremity	2	(2.0%)

Arthralgia	1	(1.0%)
Back Pain	1	(1.0%)
Bone Pain	1	(1.0%)
Flank Pain	1	(1.0%)
Muscular Weakness	1	(1.0%)
Myalgia	1	(1.0%)
Vascular Disorders	5	(5.1%)
Flushing	2	(2.0%)
Hypertension	2	(2.0%)
Deep Vein Thrombosis	1	(1.0%)
Investigations	4	(4.1%)
Blood Potassium Decreased	1	(1.0%)
Breath Sounds Abnormal	1	(1.0%)
Electrocardiogram Qrs Complex Abnormal	1	(1.0%)
Weight Decreased	1	(1.0%)
Weight Increased	1	(1.0%)
Psychiatric Disorders	4	(4.1%)
Anxiety	1	(1.0%)
Euphoric Mood	1	(1.0%)
Insomnia	1	(1.0%)
Nervousness	1	(1.0%)
Blood And Lymphatic System Disorders	3	(3.1%)
Anaemia	2	(2.0%)
Pancytopenia	1	(1.0%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	3	(3.1%)
Malignant Neoplasm Progression	1	(1.0%)
Neoplasm	1	(1.0%)
Polycythaemia Vera	1	(1.0%)
Cardiac Disorders	2	(2.0%)
Right Ventricular Hypertrophy	1	(1.0%)
Sinus Tachycardia	1	(1.0%)
Tachycardia	1	(1.0%)
Injury, Poisoning And Procedural Complications	2	(2.0%)
Radiation Injury	1	(1.0%)
Radiation Mucositis	1	(1.0%)
Metabolism And Nutrition Disorders	2	(2.0%)
Glucose Tolerance Impaired	1	(1.0%)
Hypomagnesaemia	1	(1.0%)
Renal And Urinary Disorders	2	(2.0%)
Renal Impairment	1	(1.0%)
Urinary Incontinence	1	(1.0%)
Reproductive System And Breast Disorders	1	(1.0%)
Vaginal Ulceration*	1	(1.9%)

*Gender-specific AEs: Percent based on number of patients in the specific gender.
Source: INS-05-001 Final study report, page 264-267/397 of pdf.

Table 45 shows adverse events by preferred term that occurred in >3% of the patients during the double-blind placebo-controlled cross over period. The most frequently recorded adverse event in these patients was nausea (7%), which was also the most frequently recorded adverse event during the open-label period. Adverse events occurring in >5% of these patients included hyperhidrosis and peripheral edema.

Table 45: Incidence of adverse events >3% of patients – double-blind placebo-controlled cross over period

Preferred Term	Total (N=98) n (%)
Nausea	7 (7.1)
Hyperhidrosis	5 (5.1)
Oedema peripheral	5 (5.1)
Vomiting	4 (4.1)
Cough	3 (3.1)
Diarrhoea	3 (3.1)
Headache	3 (3.1)
Urinary tract infection	3 (3.1)

Source: INS-05-001 Final study report, page 92/397 of pdf.

A composite summary of AEs associated with study drug use and mode (route) of study drug administration by maintenance (successful) dose is provided for the double-blind period in Table 46. There were 6 patients (6%) in the double-blind period that experienced an AE related to study drug use (e.g., sleepiness, dizziness, nausea, vomiting, confusion, hallucinations, weakness, shortness of breath, slow breathing or hypoventilation, slow heart rate, low blood pressure, headache, itching, rash, abdominal pain, and cold sores). Most of the AEs were observed to occur with FSS dose ≥1200 mcg. There were no patients in the double-blind period that experienced AEs related to the mode of study drug administration.

Table 46: Adverse events associated with FSS use and mode of administration – double-blind period

	100 mcg (N=4)	200 mcg (N=7)	400 mcg (N=15)	600 mcg (N=15)	800 mcg (N=24)	1200 mcg (N=20)	1600 mcg (N=13)	No Succ. Dose (N=0)	Total (N=98)
Use*	1 (25.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (15.4%)	0 (0.0%)	6 (6.1%)
Mode**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* AEs associated with study medication use: The occurrence of at least one of sleepiness, somnolence, dizziness, nausea, vomiting, confusion, confusional state, disorientation, hallucinations, weakness, shortness of breath, dyspnoea, slow breathing, hypoventilation, slow heart rate, low blood pressure, headache, itching, rash, abdominal pain, or occurrence of cold sores.
** AEs associated with mode of administration: The occurrence of at least one of sublingual erythema, edema, inflammation, difficulty swallowing, difficulty eating, application site irritation, or stomatitis.
Note: Only AEs possibly related or probably related to study medication are reported in this table.

Source: INS-05-001 Final study report, page 289/397 of pdf.

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Table 47 shows the incidence of the most common adverse events by preferred term occurring in ≥5% of patients in the titration and maintenance period of the study. The most frequently recorded adverse event was malignant neoplasm progression, which

was reported in 7 (3%) patients during the titration period and in 65 (24%) during the maintenance period. Other frequently reported AEs included vomiting, nausea, somnolence, peripheral edema, constipation, and dyspnea.

Table 47: Incidence of most common adverse events occurring in ≥5% of patients

Preferred term	Titration N=229	Maintenance N=269
	n (%)	n (%)
Malignant Neoplasm Progression	7 (3.1%)	65 (24.2%)
Vomiting	27 (11.8%)	43 (16.0%)
Nausea	30 (13.1%)	28 (10.4%)
Somnolence	23 (10.0%)	10 (3.7%)
Oedema Peripheral	7 (3.1%)	31 (11.5%)
Constipation	13 (5.7%)	28 (10.4%)
Dyspnoea	7 (3.1%)	28 (10.4%)
Asthenia	4 (1.7%)	26 (9.7%)
Fatigue	7 (3.1%)	23 (8.6%)
Application Site Irritation	17 (7.4%)	3 (1.1%)
Diarrhoea	8 (3.5%)	20 (7.4%)
Dizziness	16 (7.0%)	3 (1.1%)
Pyrexia	11 (4.8%)	18 (6.7%)
Anaemia	3 (1.3%)	17 (6.3%)
Cancer Pain	6 (2.6%)	17 (6.3%)
Anxiety	3 (1.3%)	16 (5.9%)
Back Pain	2 (0.9%)	15 (5.6%)
Anorexia	2 (0.9%)	14 (5.2%)
Dehydration	1 (0.4%)	14 (5.2%)
Cough	NA	14 (5.2%)

Source: INS-06-007 Final study report, page 74-75/808 of pdf.

During the titration period, 40 (18%) patients experienced AEs that were probably related to study drug, and 34 (15%) patients experienced AEs that were possibly related to study drug. The most common AEs, by preferred term, that were probably related to study drug included application site irritation (6%), somnolence (4%), dizziness (3%), vomiting (1%), and fatigue (1%).

During the maintenance period, 14 (5%) patients, experienced AEs that were probably related to study drug, and 52 (7%) patients experienced AEs that were possibly related to study drug. The most common AEs, by preferred term, that were probably related to study drug included constipation (<1%), nausea (<1%), withdrawal symptoms (<1%), and sedation (<1%).

There were 29 (13%) patients in the titration period that experienced an adverse event related to the mode of study drug administration. The incidence, by dose group, ranged between 7% and 22% and there did not appear to be a dose-related increase in incidence. There were 27 (10%) patients in the maintenance period that experienced an adverse event related to the mode (route) of study drug administration. The incidence, by dose group, ranged between 2% and 29%. The highest incidences occurred in the 100 mcg (12%) group and the 1600 mcg (29%) group.

7.4.2 Laboratory Findings

Clinically significant changes in clinical laboratory results were observed and expected 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 of cancer patients in the multiple-dose studies were within acceptable ranges both at baseline and post-study medication exposure. Given the lack of appropriate comparator data, the progression of disease, and the concomitant medications and therapies, these data are not interpretable.

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

INS-09-011 was an open-label single-dose pharmacodynamic study conducted in opioid-tolerant cancer patients with and without oral mucositis. Of the 9 patients in the mucositis group, 2 (22%) patients reported mild burning sensation in the oral mucosa (patient 904 had grade 1 mucositis and patient 910 had grade 2 mucositis). The Investigator judged the burning sensation in both cases to be probably related to study drug. These were the only reported adverse events in the study; no adverse events were reported from patients without mucositis. There were no increases in mucositis severity grades for any of the patients with mucositis. None of the patients without mucositis developed mucositis.

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 application.

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

A special evaluation of the study subpopulation from India in the open-label safety study INS-06-007 was conducted at the request of the Division (24 July 2007) to ensure that this subpopulation was appropriate to integrate with the remaining study population. The total number of patients in study INS-06-007 was 359, of which 77 (21.4%) were Indian patients and 282 (78.6%) patients were from other countries. There was no specific mention of Indian patients in the demographics of study INS-05-001 (130 patients in the open-label, dose-titration period and 98 patients in the double-blind placebo-controlled cross over period). However, there were two (1.5%) patients in the "Other" category during the titration period and one patient (1.0%) in the "Other" category during the double-blind period. The Applicant evaluated the incidence of treatment emergent adverse events by system organ class and preferred term in studies INS-05-001 and INS-06-007 between Indian patients and all other patients. A similar wide range of events across the major body systems was reported from both the Indian cohort and patients from other countries. The Applicant also evaluated the more common events that would provide a relative tolerability by comparing the higher frequency events (>5%) from these two demographic subgroups. The two most common events were from the gastrointestinal disorders and neurologic disorders. FSS appears to have more gastrointestinal intolerance (e.g., gastritis and abdominal pain) and less neuropsychiatric intolerance (e.g., dizziness and confusion) in the Indian cohort. There was 10.4% gastritis in the Indian cohort versus 0.0% in the cohort from other countries, and 9.1% abdominal pain in the Indian cohort versus 1.8% in the cohort from other countries. In terms of neurologic disorders, there was 0.0% dizziness in the Indian cohort versus 10.3% in the cohort from other countries, and 0.0% confusion in the Indian cohort versus 7.1% in the cohort from other countries. The significance of these observations is unclear given the Indian cohort was about 20% of the population, both gastrointestinal and neuropsychiatric disorders are high frequency adverse events in both subpopulations of the safety database, and that the general adverse events profile is similar between the two subpopulations. The Indian cohort does provide relevant safety information, and it would seem reasonable that the Indian cohort safety data be integrated with the safety data from patients of other countries.

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 FSS. 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 FSS on growth.

The Division's current thinking is to waive all pediatric studies involving fentanyl in the treatment of BTCP because the number of appropriate pediatric cancer patients is too low. This will be communicated to the Applicant.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases that were explicitly regarded as overdose. However, the following cases may be note worthy as the adverse events may suggest excessive medication.

Patient 140002 (see narrative in section 7.3.3 Dropouts and/or Discontinuations) withdrew from the study because the patient felt overmedicated from the study drug.

Patient 135001 (see narrative in section 7.3.3 Dropouts and/or Discontinuations) experienced confusion, disorientation and somnolence on Study Day 1 of the open-label period.

Patient 233017 (see narrative in section 7.3.3 Dropouts and/or Discontinuations) experienced moderate mental confusion and memory loss after achieving the 1600 mcg dose. The study drug was discontinued and the patient presented with mild withdrawal symptoms two days after study drug was discontinued.

7.7 Additional Submissions / Safety Issues

The Applicant has submitted a Risk Evaluation and Mitigation Strategy for FSS with their NDA application. The following documents have been provided:

- FSS REMS
- Prescriber Enrollment Form
- Pharmacy Enrollment Forms
- Dear Distributor Letter
- Distributor Enrollment Form
- Prescriber Knowledge Assessment
- Patient-Prescriber Agreement
- Prescriber Education Program
- Pharmacy Education Program
- Pharmacy Knowledge Assessment

In addition, the following documents in the Response to the 74-Day Filing Communication (SN0010) were provided. Except for the Medication Guide, all of the documents are the same as those filed in the single, shared REMS submitted by the Transmucosal Immediate-Release Fentanyl (TIRF) drug product application sponsors on 17 June 2011:

- Medication Guide
- Dear Prescriber Letter

- Dear Inpatient Pharmacist Letter
- Dear Outpatient Pharmacist Letter
- REMS Overview – Prescriber
- REMS Overview – Outpatient Pharmacy
- REMS Overview – Inpatient Pharmacy
- REMS Overview – Patient/Caregiver
- Distributor Enrollment Form

8 Postmarket Experience

FSS is not marketed outside the United States and has not been approved in the United States.

9 Appendices

9.1 Literature Review/References

Literature is referenced throughout the review as needed.

9.2 Labeling Recommendations

There are five previously approved 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, the FSS label should closely conform to those labels.

9.3 Advisory Committee Meeting

There is no advisory committee meeting planned for this application.

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

/s/

LUKE YIP
12/15/2011

SHARON H HERTZ
12/15/2011
I concur with a finding of safety and efficacy for this NDA.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-788 **Applicant: Insys Therapeutics, Inc** **Stamp Date: 04 March 2011**

Drug Name:
Fentanyl sublingual spray
(Proposed) Trade Name:
(b) (4)

NDA/BLA Type: 505(b)(2)
NDA

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.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
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)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
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?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			M2.5
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) Reference drug: 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: FNY-P4-270 Study Title: "A Single Site, Ascending Dose Study to Determine the Pharmacokinetics, Safety and Tolerability of a New Formulation of Fentanyl Sublingual Spray in Healthy Male Volunteers" Sample Size: 9 Arms: 2 Location in submission: Module 5 (supportive studies)				FSS 100, 400, 800 mcg and corresponding placebo without naltrexone block.
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: INS-05-001 Indication: BTCP Pivotal Study #2 Indication:	X			INS-05-001 with 4 amendments
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?	X			
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.	X			SPID30
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
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?	X			INS-06-007 with 3 amendments
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
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?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Study Report: MedDRA
24.	Has the applicant adequately evaluated the safety issues that	X			

[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
	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)?	X			Yes, for deaths, SAE; No for AE leading to discontinuation
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Mucositis study
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)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			(b) (4) [redacted]
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			M5
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			EOP2
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			SPID30 - IR to Applicant from Biometrics
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
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?			X	
FINANCIAL DISCLOSURE					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?	X			M1.3.4, Form FDA 3454
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?	X			Final study report 5.1

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

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

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

Luke Yip, MD — 28 March 2011

Reviewing Medical Officer — Date

Sharon Hertz, MD

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/

LUKE YIP
05/02/2011

SHARON H HERTZ
05/02/2011
I concur.