Fentanyl Buccal Tablet

Review and Assessment of Risks for Abuse and Diversion

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Confidentiality Statement

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1 INTRODUCTION

The fentanyl buccal tablet (FBT) is a formulation of fentanyl citrate for use by opioid-tolerant patients with breakthrough pain (BTP). Fentanyl has the potential to be abused consistent with other Schedule II opioids, and all of the commercially available dosage forms of fentanyl (parenteral, transdermal, and oral transmucosal) are listed in Schedule II of the Controlled Substances Act. Because of the potential risk for abuse, FBT is marketed under a comprehensive Risk Minimization Action Plan (RiskMAP). This plan was developed for the currently approved indication, the management of BTP in opioid-tolerant patients with cancer. This RiskMAP includes tools designed to minimize the level of abuse and to minimize diversion of FBT. The RiskMAP tools proposed are further enhanced to support a new indication, for opioid-tolerant patients with chronic pain and BTP.

Chronic opioid use represents a common treatment for patients with moderate to severe chronic pain. However, little information is available on the characteristics of this population of patients and the effects of opioid treatment over time. FBT is intended to be used as a supplemental opioid medication for the management of BTP in patients with chronic pain who are already being treated with significant doses of opioids (>60 mg/day of oral morphine or equivalent). The current clinical study database for FBT contains data from 941 opioid-tolerant patients with chronic noncancer pain and BTP treated with FBT for up to 18 months. This is one of the largest databases available for this population of patients and affords the opportunity to evaluate the more significant risks associated with chronic opioid use, ie, overdose, abuse, and diversion. The purpose of this document is to provide an assessment of these events and to explore aberrant drug-use behaviors within this population of patients to determine if predictive factors can be identified to aid in more appropriate patient selection when using a medication such as FBT. Through these assessments, it may be possible to gain a better understanding of the risk of opioid abuse within the intended population.

This document first provides a review of the events of abuse, addiction, and overdose that have been reported in FBT clinical studies of opioid-tolerant patients with chronic noncancer pain and BTP. This is followed by an assessment of aberrant drug-use behaviors identified in these studies and baseline factors that may be associated with their occurrence. Finally, a summarization of the events of diversion at both the patient level and study-center level is provided.

2 RISK FOR ABUSE

2.1 Reports of Abuse From Postmarketing Data

FBT was approved in the United States (US) on 25 September 2006 for use in patients with cancer pain and BTP. Since then, more than 83400 prescriptions have been filled. From 25 September 2006 through 19 October 2007, Cephalon received a total of 3 reports of abuse of the drug among patients prescribed the drug as follows:

- The first report (US020030) described a 34-year-old woman with a history of drug abuse and provided only limited information. She had been taking 800 mcg of FBT 3-6 times daily (indication and duration not specified). The patient experienced an overdose of FBT by taking approximately 8000 mcg (10 tablets). The patient subsequently passed out and was taken to an emergency room. The patient recovered and is seeking treatment for drug abuse.
- A second report (US021117) was received from a physician, via a sales representative, regarding an unknown number of patients (age and gender unknown) who initiated FBT therapy for the treatment of breakthrough cancer pain and subsequently may have experienced addiction. The physician stated that she may have prescribed FBT at a higher dose than the patients needed. No further information was provided. Although this case was reported as drug dependence, there is no evidence of persistent or sporadic intentional excessive use of the drug accompanied by harmful physical or psychological effects.
- A third report (US021194) was found during active review of the American Association of Poison Control Centers database (#825733). It described a 36-year-old man who had intentionally taken an undisclosed amount of FBT and experienced drowsiness/lethargy and dyspnea. The exposure was judged as potentially toxic and may have resulted in a moderate, major, or fatal outcome. The patient was lost to follow-up. No further information was provided.

It is not possible to draw any conclusions about the risk of abuse of FBT from the limited information in these few postmarketing reports.

2.2 Risk of Abuse, Addiction, and Overdose

The risk of abuse, addiction, and overdose resulting in respiratory depression is common to all opioid analgesics. However, the risk factors that lead to abuse and addiction within a population of patients with chronic pain are unclear. In the FBT clinical studies, a total of 30 patients with occurrences of high-risk events of abuse, addiction, and/or overdose were identified as follows: 13 patients had urine drug screens (UDSs) that were positive for an illicit substance or a medication for which there was no legitimate medical explanation, 9 patients had drug overdose (includes 1 patient with 2 overdoses), 7 patients were reported to have abuse/dependence, and 1 patient had abuse/dependence and an overdose (Ad Hoc Listing RA.1). The high-risk events reported in the clinical studies were evaluated to determine if common characteristics and/or risk factors were present. Review of the patients' baseline demographics and other characteristics did not reveal any factors that might aid in predicting these events. Of note, however, 9 of the 30 patients had medical history consistent with psychosis/mania. Because the incidence

(3%, 30 of 941 patients) of high-risk events was relatively low, the ability to draw conclusions based only on these data was rather limited. Therefore, a broader evaluation of predefined aberrant drug-use behaviors was undertaken as well.

With the understanding that reports from clinical studies are limited in providing a true assessment of the potential risks of abuse and addiction, a review and analysis of the FBT clinical database was undertaken with the objective of identifying possible risk factors associated with aberrant drug-use behaviors. Aberrant drug-use behaviors in patients using opioids for noncancer-related chronic pain have been used to identify patients who may be showing signs of loss of control or frank abuse and addiction. In addition, the presence of aberrant behaviors may help to identify patients who are at risk for developing abuse or addiction or having an overdose.

A retrospective evaluation of the aberrant drug-use behaviors identified in 4 clinical studies in the FBT Phase 3 program in opioid-tolerant patients with noncancer-related pain is provided herein. In addition, a number of patient characteristics were evaluated in an effort to identify those which are more likely to be associated with aberrant drug-use behaviors. The ultimate aim of such an evaluation is to provide guidance for prescribers in identifying those patients who may be at higher risk for abuse, addiction, or overdose during treatment with opioids.

2.3 Aberrant Drug-Use Behaviors in Patients With Chronic Pain

Although a number authors have published what they consider aberrant drug-use behaviors in patients with chronic noncancer-related pain (Chabal et al 1997, Ives et al 2006, Michna et al 2004, Passik et al 2002, Portenoy 1996, Webster and Webster 2005), there are no agreed upon lists of behaviors. Some aberrant behaviors are, a priori, likely more predictive of abuse and/or addiction (ie, prescription forgery, injecting an oral formulation, concurrent abuse of alcohol or illicit drugs), while others may be less egregious and more challenging to assess (ie, unsanctioned dose escalation, reporting psychic effects not intended by the treating clinician). Therefore, when evaluating aberrant behaviors, it is important to account for the severity of the behavior and the clinical situation (clinical practice vs clinical study) in which it has occurred. The following aberrant behaviors have been identified in the literature:

Selling prescription drugs
Prescription forgery
Stealing or "borrowing" drugs from others
Injection of oral formulations
Obtaining prescription drugs from nonmedical sources
Concurrent abuse of alcohol or illicit drugs
Multiple dose escalations or other noncompliance with therapy despite warnings
Multiple episodes of prescription loss
Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber or after warnings to desist
Evidence of deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use
Repeated resistance to changes in the therapy despite clear evidence of adverse physical or psychological effects from the drug
Aggressive complaining about the need for more drug
Drug hoarding during periods of reduced symptoms
Requesting specific drugs

Openly acquiring similar drugs from other medical sources
Unsanctioned dose escalations or other non-compliance with therapy on 1 or 2 occasions
Unapproved use of the drug to treat another symptom
Reporting psychic effects not intended by the clinician
Resistance to a change in the therapy associated with "tolerable" adverse events with expression of anxiety related to the return of severe symptoms
Purposely over sedating oneself
Frequency of drug intoxication
Involvement in motor vehicle accident
Requesting early renewals
Missed doctor appointment
Admitted to seeking euphoria from opioids
Admitted to wanting opioids for anxiety
Overdose and death
Injected drug
Abnormal urine/blood screen
Abnormal urine/blood positive for 2 or more substances
Requested refills instead of clinic visit
Abused prescribed drug
Was discharged from practice
No show or no follow-up
Third party required to manage patient's medication
Excessive phone calls
Concern expressed by a significant other about the patient's use of opioids
Unanticipated positive results in urine toxicology tests
Negative urine drug screen (when it is expected to be positive)
Positive urine drug screen for stimulant

Aberrant behaviors in an outpatient population receiving opioids for chronic pain are not uncommon. In a sample of 185 patients with chronic pain monitored for 1 year, 41% displayed at least 1 aberrant behavior (Webster and Webster 2005). In another study, opioid misuse occurred in 32% of patients monitored over a 1-year period (Ives et al 2006). As discussed above, the presence of these behaviors alone does not necessarily indicate abuse and/or addiction, rather it suggests that, for a substantial proportion of patients, further evaluation is warranted.

When prescribing opioids for chronic pain, it would be useful to identify patients who are at a higher risk of developing aberrant behaviors that may predict substance abuse. The ability to identify patients with chronic pain who are likely to develop these behaviors would aid in the prescribing of opioid medication and allow for appropriate precautions to be taken when they are used. Chabal et al 1997 reported that variables, such as family history of substance abuse, past problems with drugs or alcohol, a history of legal problems, dependence on cigarettes, psychiatric treatment history, multiple automobile accidents, and reporting fewer adverse symptoms, are useful in predicting aberrant behaviors. Webster and Webster 2005 identified additional risk factors such as history of sexual abuse, specific psychopathology of attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia, and depression as potential risk factors.

2.4 Assessment of Aberrant Drug-Use Behaviors in Clinical Studies of the Fentanyl Buccal Tablet

2.4.1 Patient Population

The current FBT clinical database contains patient data from 2 double-blind, placebo-controlled studies (study C25608/3041/BP/US and study C25608/3042/BP/US, hereafter referred to as study 3041 and study 3042); 1 randomized, open-label study with 3 within-patient, double-blind treatment periods (study C25608/3052/BP/US, the pivotal study, hereafter referred to as study 3052); and 1 open-label study (study C25608/3040/BP/US, hereafter referred to as study 3040) in patients with chronic noncancer pain. All of the patients who were treated in the FBT studies entered the studies while taking an around-the-clock (ATC) opioid and were managing BTP using an opioid. Typically, the BTP medication was a short-acting oral opioid medication

Patients entering the studies were either already being treated and managed within the clinical practice of the study investigator or they were recruited from outside the investigator's practice. All patients were screened and required to meet protocol-specified entry criteria. In an attempt to screen out patients who might be at higher risk of abuse and/or addiction, those with a recent history (within 5 years) or current evidence of alcohol or substance abuse were excluded. In addition, all patients underwent a urine drug screen (UDS) and were excluded if there was evidence of an illicit substance or a medication for which there was no legitimate medical explanation. Also, if in the opinion of the investigator, the patient had a psychiatric condition that would compromise the safety of the patient if they participated in the study, the patient was to be excluded. During study participation, there were no scheduled UDS samples taken (other than at the screening visit); however, the investigators were permitted to conduct a UDS at anytime at their discretion.

2.4.2 Conduct of Studies

The use of FBT in the clinical studies was on an as-needed (prn) basis; therefore, there was no predefined amount of study drug that patients were expected to use. There were limits put in place on both the number of BTP episodes that could be treated and the number of tablets that could be taken per day. In all studies, patients titrated FBT in an open-label fashion to a successful dose and were contacted daily by study center staff. Once a successful dose was determined, patients were either randomized to a double-blind treatment sequence (studies 3041 and 3042) or entered an open-label treatment period (studies 3040 and 3052) in which they were supplied with study drug and a diary for entering information about episodes experienced and tablets taken. After the first open-label treatment period study 3052, patients were randomized to a double-blind treatment sequence; this was repeated twice for a total of 3 open-label and 3 double-blind treatment periods.

Study 3040 began in March 2005 and was designed to provide long-term safety information in the intended population. It originally had a duration of participation of 12 months; however, the protocol was amended for study participation up to 18 months. Patients who entered into a long-term maintenance period were dispensed study drug and were instructed to use FBT for their BTP episodes on an as needed basis. At the initiation of the study, there were no limitations set for the number of episodes per day

for which FBT could be used or for the number of tablets that could be used in a single day. If patients ran out of study drug before a scheduled monthly visit, they were to return for another supply before the visit. The maximum number of tablets that a patient could have dispensed at any 1 time was 150. Patients were asked to complete a daily diary for recording the number of tablets taken each day and the number of BTP episodes experienced.

In April 2006, the protocol was amended to place limitations on the number of episodes for which FBT was used and number of tablets patients could take each day. With this protocol amendment, patients were limited to using FBT for no more than 6 episodes per day and taking no more than 8 tablets in a single day (allowing for taking a second dose for 2 episodes if the first dose was ineffective). This change was made due to reports that patients were using up to 11 tablets per day for BTP instead of having the dosage of their ATC opioid adjusted.

Supportive efficacy studies 3041 and 3042 had shorter durations of participation, generally less than a month. Both studies were designed to evaluate the efficacy and safety of FBT treatment compared with placebo treatment in opioid-tolerant patients with chronic pain, and had identical designs. Study 3041 included patients with a neuropathic pain and study 3042 included patients with low back pain. These studies had entry criteria similar to those for study 3040. The supply of FBT was much more limited given that patients titrated FBT to a successful dose and were then given 9 tablets of blinded study drug for the double-blind assessment of efficacy. After taking the 9^{th} tablet, the patient was to return to the study center for study completion procedures. Patients were then permitted to enter the maintenance period of study 3040 and continue participation in that study as described above.

Study 3052 is the pivotal efficacy study for a new indication. It was a 12-week open-label study with 3 double-blind, placebo-controlled efficacy periods occurring every 4 weeks after the completion of titration to a successful dose. This study enrolled opioid-tolerant patients with any type of noncancer-related pain. The entry criteria were very similar to those of the other studies, with the exceptions that ATC opioid dosage must have been stable for at least 30 days before study entry, and gas chromatography/mass spectroscopy was used for confirmatory UDS testing for screening purposes (other studies utilized immunoassay only).

Patients were to use study drug for their BTP episodes on an as needed basis throughout the study. As in study 3040, patients were limited to using FBT for no more than 6 episodes per day and were not to take more than 8 tablets per day. At visits during open-label treatment periods, patients were supplied with 150 tablets and were to report in their diaries the number of tablets taken, number of episodes experienced, and number of episodes treated each day. The maximum number of tablets that patients could have at 1 time was 150, so if patients ran out of study drug before a scheduled visit, they would have to return to the study center for another supply. As in the other studies, patients were instructed to return all unused study drug and study drug packaging at each visit. Drug accountability was done at each visit with the patient by study center staff.

2.4.3 Methods Used for Identifying Aberrant Drug-Use Behavior Data in the Clinical Database

Aberrant drug-use behaviors reported in the literature were identified in the context of clinical practice. The predictability of some of these behaviors within the structure of a clinical study is not known; however, an attempt was made to identify those behaviors that would be predictive.

As indicated above, there are a number of publications that identified aberrant drug-use behaviors within patients with noncancer-related pain who were taking opioids. These behaviors were reviewed, and those that were captured within the clinical database for FBT were identified. In addition, the behaviors were further reviewed to determine whether, in the clinical study setting, such aberrant behaviors might have face validity for potentially predicting abuse and/or addiction. The list below indicates each of the categories of behaviors to which terms identified from the clinical database were assigned.

Abuse/Dependence
Overdose
Motor vehicle accident
Fear of addiction
Discharged from practice
Positive UDS
Unreliability
Using nonprescribed medication
Study drug theft
Lost to follow-up
Seeking prescriptions from other sources
Lost study drug
Overuse of study drug
Unapproved use of a medication used for another symptom
Acquiring opioids from other medical sources

In addition to the identification of aberrant drug-use behaviors, baseline factors that may be predictive of these behaviors were identified using information from previously published studies. The factors chosen were the following:

- demographics
- pain diagnosis
- dose of ATC medication
- medical history of the following:
  - — anxiety-related disorder
  - — mood disorder
  - — psychosis/mania
  - — drug or alcohol abuse
  - — headaches

The statistical report for the assessment of the risk of abuse, addiction, and/or overdose of FBT, including the procedures followed for the identification of aberrant behaviors and baseline factors that might be predictive of these behaviors, is provided (Appendix A). Ad Hoc summary tables and a listing of patients with aberrant behaviors are also presented (Appendix B).

2.4.4 Analysis of Aberrant Drug-Use Behaviors in the Clinical Database

Of the 941 patients who took at least 1 dose of study drug (safety analysis set), 156 (17%) patients had at least 1 aberrant drug-use behavior identified through review of the database. The majority (132 of 156, 85%) of these patients had only 1 behavior identified. The aberrant behaviors identified in more than 1% of patients in the safety analysis set were overuse of study drug (44 patients, 5%), study drug theft (35 patients, 4%), and lost to follow-up (33 patients, 4%) (Table 1).

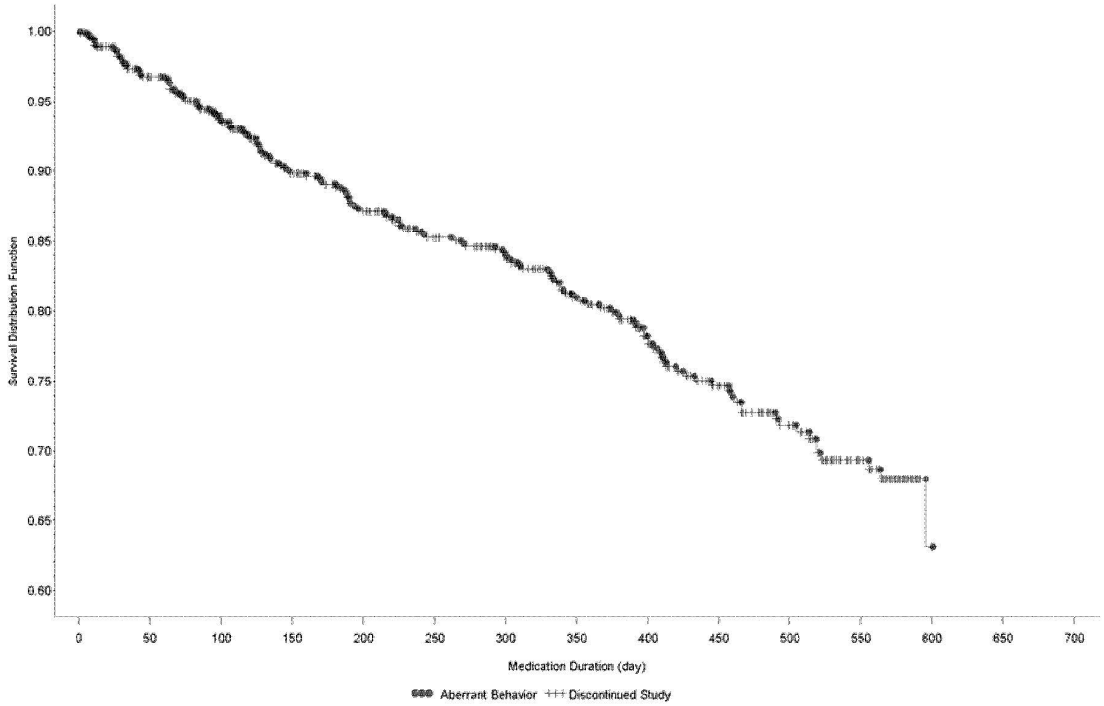
Table 1: Summary of Aberrant Drug-Use Behaviors (Safety Analysis Set)

	Number (%) of patients (N=941)				
Category of aberrant behavior	**Number of aberrant drug-use behaviors reported**				
	0	1	2	3	4
Any aberrant behavior	**785 (83)**	**132 (14)**	**19 (2)**	**4 (<1)**	**1 (<1)**
Lost to follow-up	908 (96)	33 (4)	0	0	0
Overuse of study drug	897 (95)	33 (4)	10 (1)	0	1 (<1)
Study drug theft	906 (96)	33 (4)	2 (<1)	0	0
Positive UDS	928 (99)	13 (1)	0	0	0
Overdose	931 (99)	9 (<1)	1 (<1)	0	0
Abuse/Dependence	933 (>99)	8 (<1)	0	0	0
Fear of addiction	935 (>99)	6 (<1)	0	0	0
Lost study drug	936 (>99)	5 (<1)	0	0	0
Motor vehicle accident	937 (>99)	4 (<1)	0	0	0
Using nonprescribed medication	937 (>99)	4 (<1)	0	0	0
Unapproved use of a medication to treat another symptom	939 (>99)	2 (<1)	0	0	0
Unreliability	939 (>99)	2 (<1)	0	0	0
Was discharged from practice	939 (>99)	2 (<1)	0	0	0
Acquiring opioids from other sources	940 (>99)	1 (<1)	0	0	0
Seeking prescriptions from other sources	940 (>99)	1 (<1)	0	0	0

SOURCE: Ad Hoc Summary RA.1, Ad Hoc Listing RA.1.
UDS=urine drug screen.
NOTE: Behaviors are listed in descending order by number of patients with 1 behavior reported.

The risk of having an aberrant drug-use behavior was consistent over time and did not have an association with the duration of treatment (Figure 1).

Figure 1: Time to First Onset of Aberrant Drug-Use Behavior and Withdrawal From Study (Safety Analysis Set)



SOURCE: Ad Hoc Figure RA.1.

The mean age of patients with aberrant drug-use behaviors was 45.8 years, as compared with a mean age of 49.3 years for patients with no aberrant behaviors (Table 2). Patients with significant high-risk behaviors had a mean age of 47.0 years. Consistent with the average age differences, the distribution of patients among the different age categories showed that the occurrence of aberrant drug-use behaviors was skewed towards the lower age categories. There does not appear to be a relationship between the baseline ATC daily opioid dose and aberrant drug-use behavior.

Table 2: Demographic and Baseline Characteristics by Aberrant Drug-Use Behavior (Safety Analysis Set)

Characteristic Statistic	Aberrant drug-use behavior: High risk[a] (N=30)	Aberrant drug-use behavior: All[b] (N=156)	Aberrant drug-use behavior: None (N=785)	Odds ratio (all/none)	95% CI (all–none)	p-value
Age, years						
n	30	156	785	—	—	—
Mean	47.0	45.8	49.3	—	—	—
SD	9.31	9.09	9.91	—	—	—
SE of mean	1.70	0.73	0.35	—	—	—
Median	46.5	46.0	49.0	—	—	—
Min, max	29.0, 67.0	20.0, 70.0	22.0, 77.0	—	—	—
Age group, n (%)						
≤42 years	10 (33)	55 (35)	189 (24)	2.5178	1.5, 4.3	0.0006
>42 to ≤49 years	9 (30)	50 (32)	209 (27)	2.0699	1.2, 3.6	0.0072
>49 to ≤55 years	6 (20)	28 (18)	188 (24)	1.2886	0.7, 2.3	0.3968
>55 years	5 (17)	23 (15)	199 (25)	1.0000	1.0, 1.0	—
Sex, n (%)						
Women	20 (67)	82 (53)	452 (58)	0.8164	0.6, 1.2	0.2486
Men	10 (33)	74 (47)	333 (42)	1.0000	1.0, 1.0	—
Race group, n (%)						
White	28 (93)	146 (94)	728 (93)	—	—	—
Black	1 (3)	7 (4)	40 (5)	—	—	—
Other	1 (3)	3 (2)	17 (2)	—	—	—
Primary pain diagnosis, n (%)						
Back pain	15 (50)	87 (56)	431 (55)	—	—	—
Diabetic peripheral neuropathy	2 (7)	8 (5)	31 (4)	—	—	—
Postherpetic neuralgia	0	0	5 (<1)	—	—	—
Complex regional pain syndrome	0	7 (4)	46 (6)	—	—	—
Traumatic injury	5 (17)	14 (9)	76 (10)	—	—	—
Osteoarthritis	1 (3)	8 (5)	46 (6)	—	—	—
Chronic headache	2 (7)	11 (7)	23 (3)	—	—	—
Neck pain	0	0	16 (2)	—	—	—
Fibromyalgia	0	0	12 (2)	—	—	—
Other	5 (17)	21 (13)	99 (13)	—	—	—
Primary pain diagnosis group[c], n (%)						
Neuropathic pain	7 (23)	30 (19)	161 (21)	1.0000	1.0, 1.0	—
Back pain	15 (50)	87 (56)	431 (55)	1.0833	0.7, 1.7	0.7291
Other	8 (27)	39 (25)	193 (25)	1.0845	0.6, 1.8	0.7599

Footnotes and abbreviations appear at the end of the table. (continued)

Table 2: Demographic and Baseline Characteristics by Aberrant Drug-Use Behavior (Safety Analysis Set) (Continued)

Characteristic Statistic	Aberrant drug-use behavior: High risk[a] (N=30)	Aberrant drug-use behavior: All[b] (N=156)	None (N=785)	Odds ratio (all/none)	95% CI (all–none)	p-value
Baseline ATC daily opioid dose[d], n (%)						
≤90 mg	5 (17)	36 (23)	210 (27)	4.9714	1.0, 89.9	0.1205
>90 to ≤160 mg	14 (47)	49 (31)	197 (25)	7.2132	1.5, 130.0	0.0550
>160 to ≤240 mg	3 (10)	29 (19)	192 (24)	4.3802	0.9, 79.5	0.1541
>240 mg	8 (27)	41 (26)	157 (20)	7.5732	1.5, 136.8	0.0498
Intrathecal	0	1 (<1)	29 (4)	1.0000	1.0, 1.0	—

SOURCE: Ad Hoc Summary RA.2, Ad Hoc Summary RA.3, Ad Hoc Summary RA.4, Ad Hoc Summary RA.6, Ad Hoc Listing RA.1.

[a] Includes patients with at least 1 high-risk aberrant behavior (ie, abuse/dependence, overdose, and positive urine drug screen).

[b] Includes patients with at least 1 aberrant behavior (ie, abuse/dependence, overdose, positive urine drug screen, motor vehicle accident, fear of addiction, was discharged from practice, unreliability, using nonprescribed medication, study drug theft, lost to follow-up, seeking prescriptions from other sources, lost study drug, overuse of study drug, unapproved use of a medication to treat another symptom, and acquiring opioids from other medical sources).

[c] Study 3041: all patients categorized as having neuropathic pain. Study 3042: all patients categorized as having back pain. Study 3052 and study 3040 new patients: all patients with postherpetic neuralgia, diabetic peripheral neuropathy, and complex regional pain syndrome were categorized as having neuropathic pain. All patients with back pain were categorized as back pain. All patients with diagnoses of traumatic injury, neck pain, fibromyalgia and other were categorized as having neuropathic pain if the pathophysiology of the BTP was predominantly neuropathic, otherwise they were categorized as other. All patients with diagnoses of osteoarthritis, chronic headache, and chronic pancreatitis were categorized as other.

[d] All oral opioid doses were converted to oral morphine equivalent doses before summarization according to predetermined conversion factors.

CI=confidence interval; SD=standard deviation; SE=standard error; max=maximum; min=minimum; ATC=around-the-clock; n=number of patients included in the analysis.

NOTE: The propensity for the occurrence of aberrant behavior was analyzed using logistic regression analysis.

The relationships between selected medical history abnormalities and aberrant drug-use behavior were evaluated (Table 3). Patients with medical history abnormalities associated with psychosis/mania were more than twice as likely to exhibit an aberrant behavior than patients who did not have such abnormalities.

Table 3: Medical History by Aberrant Drug-Use Behavior (Safety Analysis Set)

Medical history	Number (%) of patients with aberrant drug-use behavior: High risk[a] (N=30)	All[b] (N=156)	None (N=785)	Odds ratio (all/none)	95% CI (all–none)	p-value
Anxiety						
Yes	11 (37)	58 (37)	272 (35)	1.1162	0.8, 1.6	0.5454
No	19 (63)	98 (63)	513 (65)	1.0000	1.0, 1.0	—
Mood disorder						
Yes	16 (53)	78 (50)	438 (56)	0.7922	0.6, 1.1	0.1845
No	14 (47)	78 (50)	347 (44)	1.0000	1.0, 1.0	—
Psychosis/Mania						
Yes	2 (7)	9 (6)	21 (3)	2.2274	1.0, 4.8	0.0499
No	28 (93)	147 (94)	764 (97)	1.0000	1.0, 1.0	—
Alcohol or drug abuse						
Yes	0	1 (<1)	12 (2)	0.4156	0.0, 2.1	0.4006
No	30 (100)	155 (>99)	773 (98)	1.0000	1.0, 1.0	—

SOURCE: Ad Hoc Summary RA.5, Ad Hoc Summary RA.6.

[a] Includes patients with at least 1 high risk aberrant behavior (ie, abuse/dependence, overdose, and positive urine drug screen).

[b] Includes patients with at least 1 aberrant behavior (ie, abuse/dependence, overdose, positive urine drug screen, motor vehicle accident, fear of addiction, was discharged from practice, unreliability, using nonprescribed medication, study drug theft, lost to follow-up, seeking prescriptions from other sources, lost study drug, overuse of study drug, unapproved use of a medication to treat another symptom, and acquiring opioids from other medical sources).

CI=confidence interval.

NOTE: The propensity for the occurrence of aberrant behavior was analyzed using logistic regression analysis.

2.4.5 Conclusions

Abuse and addiction are known risks associated with all opioids. All of the patients who entered the FBT clinical studies were using ATC opioids for their persistent pain and were using short-acting opioids for the management of BTP. The 941 patients, treated for up to 18 months, represent one of the largest databases generated to date in this patient population. A total of 30 (3%) patients were identified with occurrences of abuse, addiction, and/or overdose during the studies. These cases are individually presented and discussed in the clinical study reports. The total number of observed cases of abuse was too small for an aggregate analysis of associated risk factors, and therefore, such an analysis was not performed. In an effort to evaluate behaviors that may be precursors or signs for abuse, an analysis of retrospectively defined aberrant drug-use behaviors was undertaken. Seventeen percent of patients in these studies were identified as having aberrant drug-use behaviors. This incidence is lower than those reported in the observational studies in this population (Chabal et al 1997, Webster and Webster 2005). This is likely due to the differences between clinical studies and clinical practice. Evaluation of possible baseline predictors of these behaviors revealed that younger patients and patients with medical history diagnoses consistent with mania/psychosis appear to have higher risk of displaying 1 or more of the identified aberrant behaviors. Patients who had a history of anxiety or mood disorders, which are prevalent conditions

in this population, did not appear to be at higher risk of having aberrant behaviors. In addition, the risk of developing an aberrant behavior was not affected by duration of treatment in the study.

It is important to note that these analyses are meant to evaluate behaviors that may be precursors to abuse or addiction; these behaviors do not equate to events of abuse and addiction. These results likely reflect the population studied, ie, opioid-tolerant patients with chronic noncancer-related pain and associated BTP. Clinicians treating these patients should be aware of the risk for abuse and addiction and the associated risk factors.

3 RISK OF DIVERSION

3.1 Theft of Study Drug From Patients

Thefts of study drug from 35 patients were reported in studies 3040 and 3052 (Appendix C). No patients reported thefts of study drug in studies 3041 and 3042. Police reports were made for 22 of the occurrences. Four patients (patients 024031, 042010, 043011, and 506003) enrolled in study 3040 and 1 patient (patient 002008) enrolled in study 3052 were withdrawn from the study due to the theft of fentanyl buccal tablets; patients were withdrawn when the risk of diversion or repeat theft was thought to be high. Most thefts (30 of 35) were reported to have been perpetrated by people who did not have regular access to study drug, and 20 of the thefts were reported to have occurred outside the patient's home. The frequency of thefts outside the home indicates a need to provide patients with specific instructions for safeguarding FBT in those environments. (NOTE: The husband of patient 024031 (study 3040), who was believed to have taken the patient's stud drug, was found dead of a possible FBT overdose.)

3.2 Theft of Study Drug From Study Centers

Protocols for studies with FBT stipulated that the study drug be stored at the study centers in a securely locked, substantially constructed cabinet or enclosure appropriate for a Schedule II opioid. The investigator or designee was responsible for ensuring that deliveries of study drug and other study materials from the sponsor were correctly received and recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations and local regulations. Despite these precautions, 5 study centers, all of which were participating in study 3040, reported thefts of study drug. All thefts were reported to local authorities and to the Drug Enforcement Agency per regulation. For 3 of the thefts, study drug was taken from locked cabinets, including 1 that showed signs of forced entry. In 1 case, the study drug was lost in transit from the health facility distribution center to the pharmacy, and a distribution center employee was fired as a result of the incident. In the remaining case, unused study drug returned by a patient was subsequently missing during a drug accountability/return review. All of the centers instituted additional security procedures or installed monitoring systems to lessen the risk of theft.

3.3 Conclusion

Fentanyl has the potential to be abused or diverted, consistent with other Schedule II opioids. Strict preventive measures and adherence to regulations on the part of physicians and pharmacists and detailed instructions to patients are necessary for the successful avoidance of diversion.

4 REFERENCES

Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain 1997;13(2):150-5.

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APPENDIX A
STATISTICAL REPORT

Statistical Report

Risk Assessment for

Summary of Clinical Safety for the Fentanyl Buccal Tablet in Opioid-Tolerant Patients with Breakthrough Pain

sNDA Submission

Date: 25 October 2007

Prepared by: Fang Xie, Lindsay Janka
Biostatistics Department

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1 OVERVIEW

The goal of this risk assessment analysis is to provide supportive evidence for the Abuse Liability Assessment in the Summary of Clinical Safety (SCS) for the use of the fentanyl buccal tablet (hereafter referred to as FBT) in opioid tolerant patients with noncancer-related persistent pain and breakthrough pain.

The objectives of this statistical analysis were to:

- Summarize the incidences of abuse, addiction, and/or overdose of FBT
- Summarize the incidence and types of aberrant behaviors that might be surrogates of abuse
- Explore the patient characteristics that might be possibly predictive of aberrant behaviors

2 THE DATA

Due to the controlled nature of the clinical trials, the relatively low overall incidence of reported abuse, addiction, and overdose limits the ability to make broad generalizations. Aberrant drug related behaviors have been widely used as potential precursors or indicators for patients who may be showing signs of loss of control or frank abuse and addiction. To allow for assessment of risk, aberrant behaviors were identified through extensive review of the FBT clinical trial database. Potentially important demographic and baseline characteristics were also identified and were incorporated into the analysis.

The scope of the database search was the integrated safety database for SCS that contains 4 studies (3040, 3041, 3042, and 3052).

2.1 Identifying Aberrant Behaviors

Aberrant behaviors have been described extensively in the medical literature (see References). A list of aberrant drug related behaviors were predefined through a review of the literature. Listings from the datasets in the subsequent sections were reviewed by Cephalon medical experts for the presence of possible aberrant behaviors. From this review, a list of target terms was compiled and was used by the Cephalon Biostatistics Department to conduct text string searches within those datasets. Results of the search along with necessary details such as verbatim text were manually reviewed again by the medical experts for false positive and duplicate results. The results from the various datasets were compiled into a final listing of the aberrant behaviors. The identified behaviors were then classified by Cephalon medical experts into categories consistent with that reported within literature. Finally, patients were identified as with and without any aberrant behaviors for analysis.

2.1.1 Adverse Events

Adverse events have been coded using the MedDRA 8.1 dictionary. The following terms were used as text strings in the search of the adverse event database for potential aberrant behaviors:

Dependence
Drug dependence
Polysubstance dependence
Intentional misuse
Overdose
Multiple drug overdose
Multiple drug overdose accidental
Intentional misuse
Multiple drug overdose intentional
Accidental overdose
Poisoning
Drug intoxication
Unresponsive to pain stimuli
Unresponsive to verbal stimuli

Drug interaction
Road traffic accident
Polytraumatism
Accidental exposure
Suicide attempt

2.1.2 Noncompliance

For patients who discontinued the studies for non-compliance with the study procedures or study drug, all reports were reviewed manually by Cephalon medical experts. Cases where an aberrant behavior may have occurred were identified. In addition, the following strings of text were searched in the verbatim of the case report form (CRF) noncompliance and termination pages:

lost
losing
seek
source
opioid
alternative
misuse
abuse
overuse

2.1.3 Protocol Violations

For patients with reported protocol violations, all reports were reviewed manually by Cephalon medical experts. Cases where an aberrant behavior may have occurred were identified. In addition, the following strings of text were searched in the verbatim of the CRF protocol violation and termination pages:

uds
urine drug screen
udt
drug screen
urine screen
positive screen
positive urine
screen urine
screen drug
urine drug
seek
source
opioid
alternative
misuse
abuse

overuse
history

2.1.4 Study Medication Theft

All cases of medication theft were considered as aberrant behaviors. In addition, the following terms were searched in the database verbatim:

stole
theft

2.1.5 Study Drug Usage

For safety considerations, Cephalon implemented a daily maximum allowance of 8 FBT tablets on April 12, 2006. A search was conducted to identify the patients who (after May 1, 2006) took more than 8 tablets per day on average during at least 2 visit intervals in the posttitration period.

2.1.6 Other Text

For thoroughness, additional search of the entire safety database was conducted for the following terms:

addic
abuse
drug use
uds
overuse
stol

2.2 Categorizing Aberrant Behavior

The search results were further classified into the following 15 categories of aberrant behavior by Cephalon medical experts based on descriptions of aberrant behaviors in the medical literature:

1. Abuse/dependence
2. Overdose
3. Motor Vehicle Accident
4. Fear of Addiction
5. Was Discharged from Practice
6. Positive UDS
7. Unreliability
8. Using non-prescribed medication
9. Medication Theft
10. Lost to Follow-up
11. Seeking prescriptions from other sources
12. Lost Study medication
13. Overuse of study medication including >8 tablets per day
14. Unapproved use of drug to treat another symptom

15. Acquiring opioids from other medical sources

Three categories, Abuse/dependence, Overdose, and Positive UDS, were considered to represent high risk events.

A binary variable was created to indicate each patient having or not having any aberrant behaviors. Another variable was similarly created for the high risk behaviors.

2.3 Predictors

2.3.1 Baseline Characteristics

The inclusion of baseline characteristics was in accordance with the most recent research publications (Reference). They included:

- age groups defined by quartile
- gender
- race
- BMI groups defined by quartile
- pain diagnosis
- pathophysiology of the breakthrough pain
- pain medication
- baseline ATC daily dose defined by quartile
- baseline SF-36 physical composite score defined by quartile and by median
- baseline SF-36 mental composite score defined by quartile
- baseline POMS total mood score defined by quartile

2.3.2 Medical History

Abnormal medical history within the CRF fields of psychiatric history and neurologic history was reviewed by Cephalon Medical Experts. Each unique verbatim description was reviewed for the presence of the following diagnoses, and/or components of these diagnoses:

Abnormal neurologic history of:

- headache

Abnormal psychiatric history of:

- mood disorder
- anxiety disorder
- psychosis/mania
- history of abuse

3 STATISTICAL METHODS

This risk assessment analysis is observational and exploratory in nature. Analysis results are limited to the observations in clinical trial database. Caution should be exercised in generalizing the results to the entire patient population.

3.1 Data Summary

Demographics, baseline characteristics, and relevant medical history were summarized by the indicators of aberrant behaviors and high risk behaviors using descriptive statistics. The Kaplan-Meier curve was used to illustrate the time course of the fist onset of the aberrant behaviors.

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error (SE) of the mean, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

Patients with any aberrant behaviors were listed with their unique patient identifier, aberrant behavior category, high risk event flag, and study day.

3.2 Exploratory Modeling

3.2.1 The Rationale

It was hypothesized that the aberrant behaviors observed during the clinical trials might be precursors or indicators of potential signs for patients who may loss of control or frank abuse and addiction. It was also hypothesized that relevant baseline characteristics and medical conditions prior to entering the clinical studies might be associated or even predictive of aberrant behaviors. There are a large number of baseline characteristics and medical conditions in the database and many of them are related to one another. It was of interest to develop a statistical model that could relate the aberrant behaviors with multiple baseline characteristics that are minimally confounding each other so that appropriate warnings or guidance could be provided to healthcare professionals in order to lower the risk of abuse or overdose.

The objective of the modeling was to estimate the incidence rate of aberrant behaviors on the basis of multiple patient characteristics. The analysis was not inferential. The estimations are limited to the clinical safety database that was assembled from the trials conducted in non-cancer patients.

3.2.2 Modeling the Incidence of Aberrant Behaviors

As the high risk behaviors occurred at a low rate, descriptive statistics were considered adequate to summarize those high risk behaviors and the modeling was performed for the broader definition of aberrant behaviors.

A binary variable was created to indicate each patient having or not having aberrant behaviors in at least one of the categories (see section 2.2). The incidence of any aberrant behavior was assumed to follow a binomial distribution and the logistic regression model

was used to quantify the relationship between the incidence rate of aberrant behaviors and the baseline characteristics. This incidence rate is linked to the risk factors through the logit function. The parameters were estimated using the maximum likelihood method. The statistical test used was the likelihood ratio based F-test for the Type 3 analysis. The significance level for the final model fitting was 0.10. The goodness of fit for the final main effect model was evaluated by the ratio of deviance over degrees of freedom and the scaled Pearson Chi-square statistics.

Given a combination of baseline characteristics, the incidence rate of aberrant behaviors was estimated along with the 95% confidence interval from the final model. Each parameter is a log odds ratio. The odds ratio was calculated by exponentiation of the parameter. An odds ratio measures the difference of a particular level relative to the reference level of the characteristic. In order to estimate the incidence rate, one needs to calculate the exponentiation of the linear combinations of the parameter estimates from the final model. Then, the incidence rate can be estimated by taking the anti-logit transformation for the exponentiation of the linear combination. Confidence limits can be estimated in the same fashion from the corresponding confidence limits for the linear combination.

3.2.3 Modeling Procedure

A stepwise procedure is employed in the modeling process because of the large number of factors to be considered.

In the initial screening, a single factor logistic model was performed for each risk factor. Through the screening, factors were classified into 3 groups by the p-values for the factor that was obtained by the likelihood ratio test. The 3 groups were: 1) p-value <= 0.05, 2) p-value is 0.05 – 0.10, 3) p-value > 0.10. Factors in the third group were eliminated from further exploration and declared to be not associated with the aberrant behaviors.

Next, multi-factor models were fit. Through the modeling, correlated or confounding factors were eliminated. The beginning model was a main effect model that included all factors found in the screening step with p-values <= 0.10. A backward elimination procedure was followed to remove the least significant factor from the model at each time. The final main effect model was obtained once the non significant factors were eliminated at the significance level of 0.10.

In addition to the final main effect model, models including 2-way interaction terms were explored. These models included the interactions between each pair of factors in the final main effect model. The interaction model was finalized through the step-down process.

4 RESULTS

4.1 Aberrant Behaviors

There were totally 941 patients in the integrated safety database who were exposed to FBT at least once during the 4 clinical trials (3040, 3041, 3042, and 3052). According to the aberrant behaviors described previously, 156 patients (17% of 941) were identified to have exhibited at least one aberrant behavior. Table 1 tabulates the frequencies of aberrant behaviors that were identified from the integrated safety database.

Table 1. Frequency of Aberrant Behaviors per Patient

Frequency	Number of Patients (N=941)	Percent
0	785	83%
1	132	14%
2	19	2%
3	4	<1%
4	1	<1%

Source: Ad Hoc Summary RA.1, Ad Hoc Listing RA.1

Each patient was classified into a unique category based on the risk level of the aberrant behaviors as described in section 2.2. Table 2 summarizes the patients by the aberrant behavior risk category.

Table 2. Summary of Patients by Risk Category

Risk Category	Number of Patients (N=941)	Percent
High risk behaviors*	30	3%
Abuse/dependence	8	<1%
Overdose	10	1%
Positive UDS	13	1%
Other Aberrant behaviors	126	13%
None	785	83%

Source: Ad Hoc Summary RA.1, Ad Hoc Listing RA.1
* 3 patients also had non-high risk aberrant behaviors

The Kaplan-Meier curves below illustrate the first onset of aberrant behaviors and the first onset of high risk aberrant behaviors over time. For both, the rate of onset seemed to be nearly constant over the course of 600 days.

Figure 1. Time to First Onset of Aberrant Behavior

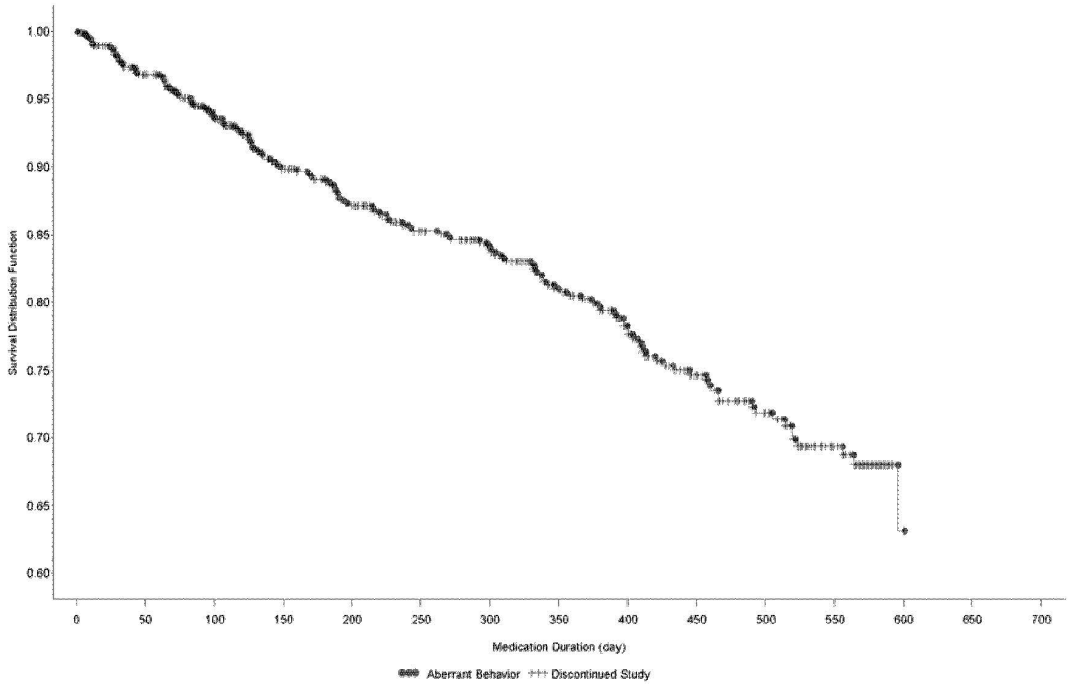
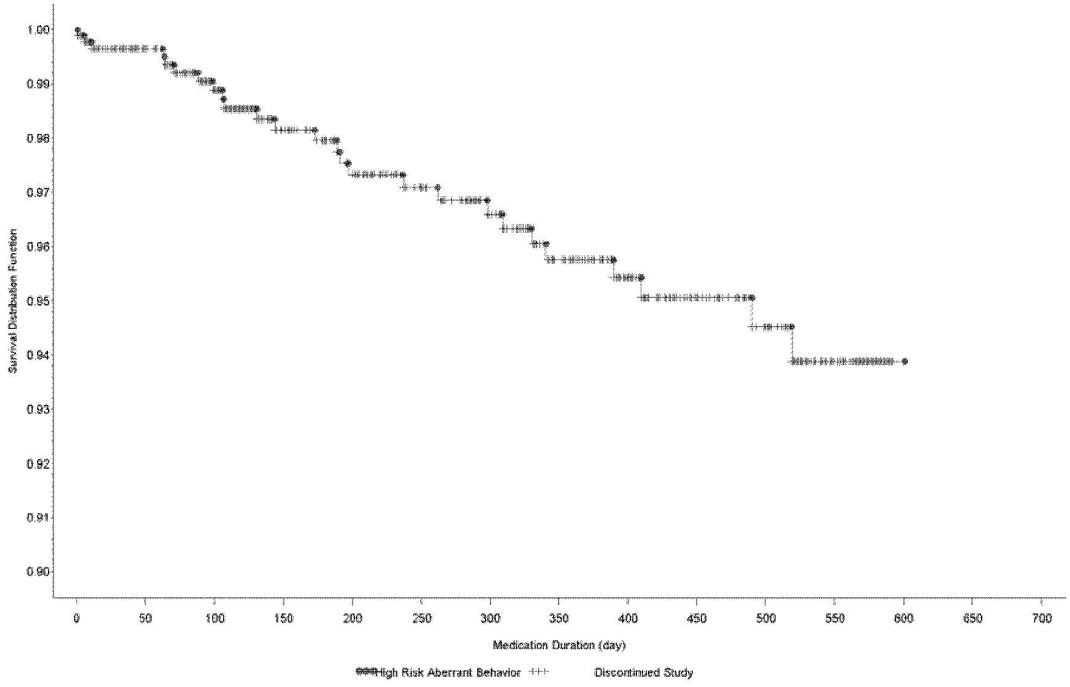


Figure 2. Time to First Onset of High Risk Aberrant Behavior



4.2 Patient Characteristics

Summary statistics were presented by risk category for demographics and baseline characteristics in Ad Hoc Summary RA.2 through Ad Hoc Summary RA.5.

Differences were seen in the descriptive statistics in age and medical history between patients who had aberrant behaviors versus who did not.

4.3 Modeling the Incidence Rate

4.3.1 Screening the Characteristics

Through the single factor logistic regression model, the following characteristics of the patients were explored and grouped by statistical significance level as described in section 3.2.3. Detailed analysis results are summarized in Ad Hoc Summaries RA.6.

Table 3. Single Factors Screened

Factor	Categories	Reference Level	p-value
Age quartiles	<=42 yrs >42 to <=49 yrs >40 to <=55 yrs >55 yrs	> 55 years	<0.05
Race group	White Black Other	Other	>0.10
Sex	Male Female	Male	>0.10
BMI quartiles	<=24.80 >24.80 - <=29.14 >29.14 - <=34.20 >34.20 Missing	<=24.80	>0.10
Baseline SF-36 physical composite score quartiles	<=22.24 >22.24 - <=26.00 >26.00 - <=31.50 >31.50 Missing	>31.50	>0.05 to <=0.10
Baseline Sf-36 mental composite score quartiles	<=34.49 >34.49 - <=40.75 >40.75 - <=51.56 >51.56 Missing	>51.56	>0.10
Baseline SF-36 physical composite score by median	<=26.00 >26.00 Missing	>26.00	<0.05
Baseline Sf-36 mental composite score by median	<=40.75 >40.75 Missing	>40.75	>0.10
Baseline POMS total mood score quartiles	<=6.00 >28.00 - <=54.00 >54.00 >6.00 - <=28.00 Missing	<=6.00	>0.10

Factor	Categories	Reference Level	p-value
History of Mood	Yes No	No	>0.10
History of Anxiety	Yes No	No	>0.10
History of Psychosis/Mania	Yes No	No	<0.05
History of abuse	Yes No	No	>0.10
History of headaches	Yes No	No	>0.10
Primary pain diagnosis group	Back pain Neuropathic pain Other	Neuropathic pain	>0.10
Pathophysiology of the primary pain	Predominantly neuropathic Predominantly nociceptive Mixed Missing/Not collected	Predominantly neuropathic	>0.10
Baseline ATC daily dose quartiles	<=90 >90 - <=160 >160 - <=240 >240 Intrathecal	Intrathecal	<0.05

Source: Ad Hoc Summary RA.6

4.3.2 The Final Model

The significant factors were not all independent of each other. Therefore, some of the factors became not significant in the model with all these factors included.

Following the model selection procedure described in section 3.2.3, the patient characteristics in Table 3 were reduced and confounding factors were eliminated. Age quartiles and baseline ATC daily dose quartiles were found to be statistically significant (p-value <= 0.10) in the final main effect model. History of psychosis /mania was also significant (p-value < 0.10) when the second (>90 – <=160) and fourth (>240) ATC quartiles were combined based on their significance in the model. Based on its clinical relevance and statistical significance, history of psychosis/mania was also included in the final model. The finding suggests that the risk model for aberrant behavior is more complex than a single contributing factor. Within the limit of the clinical safety database, each of the above 3 factors or a combination of them contributed to the risk of exhibiting aberrant behaviors.

The ratio of deviance over the degrees of freedom and the scaled Pearson Chi-square statistics were 0.95 and 0.90, respectively, for the final model. These statistics indicated no sign of over-dispersion in the final model.

In addition, the interaction model was explored to test the significance of all possible 2-way interactions between the above 3 factors. The 2-way interactions were either

statistically not significant or causing model fail to converge. The main effect model with the 3 main effects was considered as final.

4.3.3 Parameter Estimates

The parameter estimates from the final model are listed in Table 4:

Table 4. Final Model Parameter Estimates and 95% Confidence Intervals

Parameter	Category	Estimate	95% Confidence Limits		Pr > ChiSq
Intercept		-3.8030	-6.7029	-2.2018	0.0002
Age Group	<=42 yrs	0.8646	0.3449	1.4116	0.0014
	>42 to <=49 yrs	0.6917	0.1670	1.2419	0.0113
	>49 to <=55 yrs	0.2314	-0.3578	0.8293	0.4425
Baseline ATC daily dose quartiles	<=90	1.4956	-0.1058	4.3934	0.1488
	>90 - <=160	1.4032	-0.2075	4.3037	0.1767
	>160 - <=240	1.8652	0.2666	4.7622	0.0715
	>240	1.9046	0.3162	4.7986	0.0649
History of psychosis /mania	Yes	0.6525	-0.2092	1.4384	0.1162

The estimate of intercept (-3.8, p-value = 0.0002) means that there is a significant incidence rate of aberrant behaviors in the patient category with all characteristics at the reference level (>55 yrs for age group, on intrathecal ATC at baseline, "No" for history of psychosis /mania). This model suggests that the incidence rate is likely around 2% with the 95% CI of (0.1%, 10%) for patients who are older than 55 years, with intrathecal ATC, and with no history of psychosis /mania.

The fact that the estimates for all parameters in Table 4 are positive indicates an increase in the incidence rate of aberrant behaviors for patients who possess characteristics other than the reference levels. For example, the incidence rate is estimated to be 4% (95% CI: 0.01% to 32%) for patients who are older than 55 years, with intrathecal ATC, but had a history of psychosis /mania. This rate is estimated to be 9% (95% CI: 0.01% to 66%) if the patient are younger than 42 years of age, with a baseline ATC daily dose >240 mg, and with a history of psychosis /mania.

The risk of exhibiting aberrant behavior for a particular patient characteristic relative to the reference level is estimated by the odds ratios. An odds ratio greater than 1 suggests an increase in risk from the reference level. Section 3.2.2 describes the method for converting the model parameter estimates to odds ratios. Table 5 summarizes the odds ratio estimates from the final model.

Table 5. Odd Ratio Estimates

Patient Characteristic	Category	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Age Quartiles	<=42 yrs	55 (35)	189 (24)	2.3741	(1.4, 4.1)	0.0014
	>42 to <=49 yrs	50 (32)	209 (27)	1.9970	(1.2, 3.5)	0.0113
	>49 to <=55 yrs	28 (18)	188 (24)	1.2604	(0.7, 2.3)	0.4425
	>55 yrs	23 (15)	199 (25)	1.0000	(1.0, 1.0)	
Baseline ATC daily dose quartiles	<=90	36 (23)	210 (27)	4.4619	(0.9, 80.9)	0.1488
	>160 - <=240	29 (19)	192 (24)	4.0681	(0.8, 74.0)	0.1767
	>240	41 (26)	157 (20)	6.4575	(1.3, 117.0)	0.0715
	>90 - <=160	49 (31)	197 (25)	6.7168	(1.4, 121.3)	0.0649
	Intrathecal	1 (<1)	29 (4)	1.0000	(1.0, 1.0)	
History of Psychosis/Mania	No	147 (94)	764 (97)	1.0000	(1.0, 1.0)	
	Yes	9 (6)	21 (3)	1.9203	(0.8, 4.2)	0.1162

Source: Ad Hoc Summary RA.7

4.4 Remarks

Note that the 95% confidence interval widens rapidly as the number of characteristics to be considered. This means, the estimation precision decreases as the number of characteristics increases.

The presented analysis is observational and limited by the clinical safety database. Therefore, the result interpretation requires caution.

5 REFERENCES

Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain 1997;13(2):150-5.

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Michna E, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. J Pain Symptom Manage 2004;28(3):250-8.

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Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996;11(4):203-17.

Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005;6(6):432-42.

6 LIST OF AD HOC SUMMARIES, LISTINGS, AND FIGURES

6.1 Ad Hoc Summary Tables

Ad Hoc Summary number	Title
RA.1	Overall Summary of Aberrant Behaviors by Category
RA.2	Demographics and Baseline Characteristics by Aberrant Behavior Categories
RA.3	Primary Pain Diagnosis by Aberrant Behavior Categories
RA.4	Pain Medications at Baseline by Around-the-Clock (ATC) Type by Aberrant Behavior Categories
RA.5	Aberrant Medical History Drug Predictors by Aberrant Behavior Categories
RA.6	Odds Ratio of Aberrant Behaviors by Patient Characteristics
RA.7	Final Main Effect Model: Odds Ratio of Aberrant Behaviors by Patient Characteristics

6.2 Ad Hoc Individual Patient Listings

Ad Hoc Listing number	Title
RA.1	Aberrant Behavior Categories

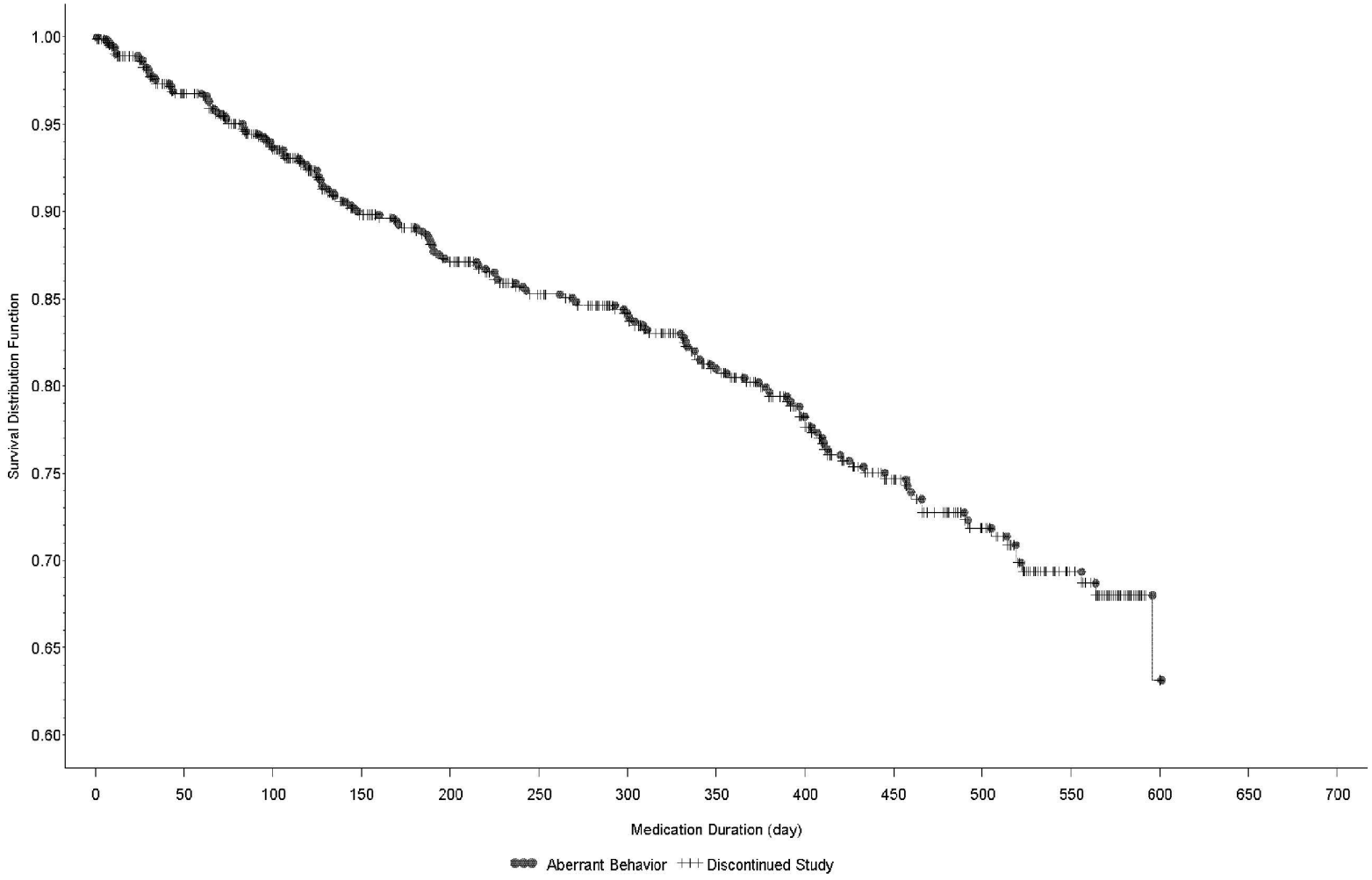
6.3 Ad Hoc Figures

Ad Hoc Figure number	Title
RA.1	Time to First Onset of Aberrant Behavior
RA.2	Time to First Onset of High Risk Aberrant Behavior

APPENDIX B
SUPPORTIVE FIGURES, SUMMARY TABLES, AND LISTINGS

List of Supportive Figures

Ad Hoc Figure RA.1
Time to First Onset of Aberrant Behavior
Safety Analysis Set



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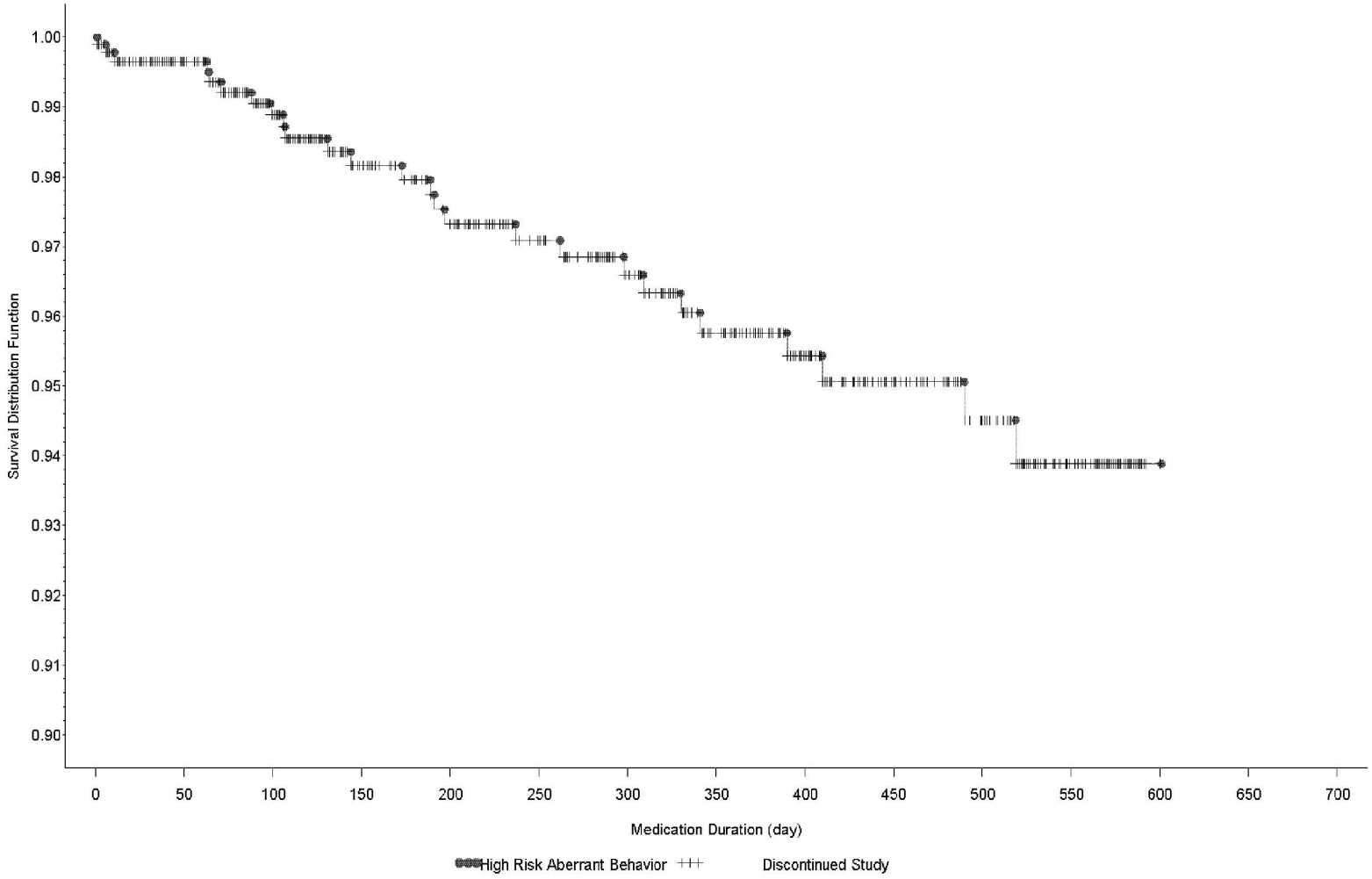
Ad Hoc Figure RA.2
Time to First Onset of High Risk Aberrant Behavior
Safety Analysis Set



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List of Summary Tables

Ad Hoc Summary RA.1
Overall Summary of Aberrant Behaviors by Category
Safety Analysis Set

Variable Statistic	Total (N=941)
Number of high risk aberrant behaviors	
0	911 (97)
1	28 (3)
2	2 (<1)
3	0
4	0
Number of any aberrant behaviors	
0	785 (83)
1	132 (14)
2	19 (2)
3	4 (<1)
4	1 (<1)
Abuse/dependence	
0	933 (>99)
1	8 (<1)
2	0
3	0
4	0
Acquiring opioids from other sources	
0	940 (>99)
1	1 (<1)
2	0
3	0
4	0
Fear of addiction	
0	935 (>99)
1	6 (<1)
2	0
3	0
4	0

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk1.sas (FX) Data Extract: 10/25/07 16:24 Table Generation: 10/26/07 8:41

Ad Hoc Summary RA.1
Overall Summary of Aberrant Behaviors by Category
Safety Analysis Set

Variable Statistic	Total (N=941)
Lost study medication	
0	936 (>99)
1	5 (<1)
2	0
3	0
4	0
Lost to follow-up	
0	908 (96)
1	33 (4)
2	0
3	0
4	0
Medication theft	
0	906 (96)
1	33 (4)
2	2 (<1)
3	0
4	0
Motor vehicle accident	
0	937 (>99)
1	4 (<1)
2	0
3	0
4	0
Overdose	
0	931 (99)
1	9 (<1)
2	1 (<1)
3	0
4	0

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk1.sas (FX) Data Extract: 10/25/07 16:24 Table Generation: 10/26/07 8:41

Ad Hoc Summary RA.1
Overall Summary of Aberrant Behaviors by Category
Safety Analysis Set

Variable Statistic	Total (N=941)
Overuse of study medication	
0	897 (95)
1	33 (4)
2	10 (1)
3	0
4	1 (<1)
Postive UDS	
0	928 (99)
1	13 (1)
2	0
3	0
4	0
Seeking prescriptions from other sources	
0	940 (>99)
1	1 (<1)
2	0
3	0
4	0
Unapproved use of drug to treat another symptom	
0	939 (>99)
1	2 (<1)
2	0
3	0
4	0
Unreliability	
0	939 (>99)
1	2 (<1)
2	0
3	0
4	0

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk1.sas (FX) Data Extract: 10/25/07 16:24 Table Generation: 10/26/07 8:41

Ad Hoc Summary RA.1
Overall Summary of Aberrant Behaviors by Category
Safety Analysis Set

Variable Statistic	Total (N=941)
Using non-prescribed medication	
0	937 (>99)
1	4 (<1)
2	0
3	0
4	0
Was discharged from practice	
0	939 (>99)
1	2 (<1)
2	0
3	0
4	0

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk1.sas (FX) Data Extract: 10/25/07 16:24 Table Generation: 10/26/07 8:41

Ad Hoc Summary RA.2
Demographics and Baseline Characteristics by Aberrant Behavior Categories
Safety Analysis Set

Variable Statistic	Aberrant Behavior: High Risk (N=30)	All Aberrant (N=156)	None (N=785)	Total (N=941)
Age (yrs)				
n	30	156	785	941
Mean	47.0	45.8	49.3	48.7
SD	9.31	9.09	9.91	9.86
SE of mean	1.70	0.73	0.35	0.32
Median	46.5	46.0	49.0	49.0
Min, max	29.0, 67.0	20.0, 70.0	22.0, 77.0	20.0, 77.0
Age quartiles, n (%)				
<=42	10 (33)	55 (35)	189 (24)	244 (26)
>42 to <=49	9 (30)	50 (32)	209 (27)	259 (28)
>49 to <=55	6 (20)	28 (18)	188 (24)	216 (23)
>55	5 (17)	23 (15)	199 (25)	222 (24)
Sex, n (%)				
Male	10 (33)	74 (47)	333 (42)	407 (43)
Female	20 (67)	82 (53)	452 (58)	534 (57)
Race, n (%)				
White	28 (93)	146 (94)	728 (93)	874 (93)
Black	1 (3)	7 (4)	40 (5)	47 (5)
Asian	1 (3)	1 (<1)	0	1 (<1)
American Indian or Alaskan Native	0	0	4 (<1)	4 (<1)
Pacific Islander	0	0	0	0
Other	0	2 (1)	13 (2)	15 (2)
Race group, n (%)				
White	28 (93)	146 (94)	728 (93)	874 (93)
Black	1 (3)	7 (4)	40 (5)	47 (5)
Other	1 (3)	3 (2)	17 (2)	20 (2)

Notes: For rollover patients in study C25608/3040/BP/US, demographics and baseline characteristics were collected in study C25608/3041/BP/US or C25608/3042/BP/US.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\XSSCSDEMAB.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.2
Demographics and Baseline Characteristics by Aberrant Behavior Categories
Safety Analysis Set

Variable Statistic	Aberrant Behavior: High Risk (N=30)	All Aberrant (N=156)	None (N=785)	Total (N=941)
Weight (kg)				
n	29	155	784	939
Mean	88.3	86.4	88.7	88.3
SD	25.61	23.05	25.27	24.92
SE of mean	4.76	1.85	0.90	0.81
Median	87.1	83.9	84.9	84.8
Min, max	49.0, 167.8	47.6, 185.9	43.5, 284.4	43.5, 284.4
Height (cm)				
n	29	155	778	933
Mean	169.6	171.4	170.6	170.8
SD	8.34	10.24	10.28	10.27
SE of mean	1.55	0.82	0.37	0.34
Median	168.9	170.2	170.2	170.2
Min, max	156.2, 190.5	142.2, 200.7	135.7, 203.2	135.7, 203.2
BMI (kg/m^2)				
n	29	155	778	933
Mean	30.4	29.3	30.3	30.2
SD	7.33	7.01	7.97	7.83
SE of mean	1.36	0.56	0.29	0.26
Median	30.5	28.6	29.3	29.1
Min, max	18.5, 46.2	16.7, 63.3	14.3, 76.3	14.3, 76.3
BMI quartiles (kg/m^2)				
<=24.80	5 (17)	39 (25)	195 (25)	234 (25)
>24.80 - <=29.14	9 (30)	45 (29)	188 (24)	233 (25)
>29.14 - <=34.20	6 (20)	38 (24)	197 (25)	235 (25)
>34.20	9 (30)	33 (21)	198 (25)	231 (25)
Missing	1 (3)	1 (<1)	7 (<1)	8 (<1)

Notes: For rollover patients in study C25608/3040/BP/US, demographics and baseline characteristics were collected in study C25608/3041/BP/US or C25608/3042/BP/US.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\XSSCSDEMAB.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.3
Primary Pain Diagnosis by Aberrant Behavior Categories
Safety Analysis Set

Variable Statistic, n (%)	Aberrant Behavior High Risk (N=30)	 All Aberrant (N=156)	 None (N=785)	 Total (N=941)
Primary pain diagnosis				
Back pain	15 (50)	87 (56)	431 (55)	518 (55)
Diabetic peripheral neuropathy (DPN)	2 (7)	8 (5)	31 (4)	39 (4)
Postherpetic neuralgia (PHN)	0	0	5 (<1)	5 (<1)
Complex regional pain syndrome	0	7 (4)	46 (6)	53 (6)
Traumatic injury	5 (17)	14 (9)	76 (10)	90 (10)
Osteoarthritis	1 (3)	8 (5)	46 (6)	54 (6)
Chronic headache	2 (7)	11 (7)	23 (3)	34 (4)
Neck pain	0	0	16 (2)	16 (2)
Fibromyalgia	0	0	12 (2)	12 (1)
Chronic pancreatitis	0	0	0	0
Other	5 (17)	21 (13)	99 (13)	120 (13)
Primary pain diagnosis group				
Neuropathic pain	7 (23)	30 (19)	161 (21)	191 (20)
Back pain	15 (50)	87 (56)	431 (55)	518 (55)
Other	8 (27)	39 (25)	193 (25)	232 (25)
Pathophysiology of the BTP				
Predominantly neuropathic	11 (37)	47 (30)	228 (29)	275 (29)
Predominantly nociceptive	7 (23)	49 (31)	238 (30)	287 (30)
Mixed	7 (23)	44 (28)	229 (29)	273 (29)
Not collected	5 (17)	16 (10)	88 (11)	104 (11)
Missing	0	0	2 (<1)	2 (<1)

Notes: A patient can be counted only once in any primary painful condition category, only once in any primary pain diagnosis group, and only once in any pathophysiology of the BTP. The pathophysiology of the BTP was not collected in study C25608/3042/BP/US.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\XSSCSPAINAB.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.4
Pain Medications at Baseline by Around-the-Clock (ATC) Type by Aberrant Behavior Categories
Safety Analysis Set

Aberrant behavior: High Risk

Type Statistic	Patients Taking Oral Opioids	Patients Taking Transdermal Fentanyl	Total
ATC medication (mg/day)			
n	25	5	30
Mean	215.6	184.8	210.4
SD	143.98	131.89	140.33
SE of mean	28.80	58.98	25.62
Median	120.0	120.0	120.0
Min, max	80.0, 480.0	120.0, 420.0	80.0, 480.0
Rescue medication (mg/BTP)			
n	24	5	29
Mean	34.1	48.4	36.6
SD	29.53	43.96	31.98
SE of mean	6.03	19.66	5.94
Median	20.0	30.0	20.0
Min, max	10.0, 120.0	12.0, 120.0	10.0, 120.0
Baseline ATC daily dose (mg), n (%)	25 (100)	5 (100)	30 (100)
<=90	5 (20)	0	5 (17)
>90 - <=160	10 (40)	4 (80)	14 (47)
>160 - <=240	3 (12)	0	3 (10)
>240	7 (28)	1 (20)	8 (27)
Intrathecal	0	0	0

Notes: Patients using intrathecal opioids were not summarized in ATC or total since these opioids were not converted to morphine equivalents. All non-intrathecal doses are converted to oral morphine equivalents prior to summarization. ATC medication summary statistics are calculated from daily patient totals and rescue medication summary statistics are calculated from average patient uses. Only data from each patient's first study is included here.
Baseline ATC daily dose categories are determined from quartiles.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\Xsscspmedab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.4
Pain Medications at Baseline by Around-the-Clock (ATC) Type by Aberrant Behavior Categories
Safety Analysis Set

Aberrant behavior: All Aberrant

Type Statistic	Patients Taking Oral Opioids	Patients Taking Transdermal Fentanyl	Patients Taking Intrathecal Medications	Total
ATC medication (mg/day)				
n	124	31	1	155
Mean	223.5	220.0		222.8
SD	210.72	135.32		197.57
SE of mean	18.92	24.31		15.87
Median	120.0	180.0		160.0
Min, max	20.0, 1440.0	60.0, 720.0		20.0, 1440.0
Rescue medication (mg/BTP)				
n	123	31	1	155
Mean	25.9	33.2	20.0	27.4
SD	18.73	31.10	.	21.80
SE of mean	1.69	5.59	.	1.75
Median	20.0	20.0	20.0	20.0
Min, max	9.6, 120.0	10.0, 150.0	20.0, 20.0	9.6, 150.0
Baseline ATC daily dose (mg), n (%)	124 (100)	31 (100)	1 (100)	156 (100)
<=90	34 (27)	2 (6)	0	36 (23)
>90 - <=160	40 (32)	9 (29)	0	49 (31)
>160 - <=240	15 (12)	14 (45)	0	29 (19)
>240	35 (28)	6 (19)	0	41 (26)
Intrathecal	0	0	1 (100)	1 (<1)

Notes: Patients using intrathecal opioids were not summarized in ATC or total since these opioids were not converted to morphine equivalents. All non-intrathecal doses are converted to oral morphine equivalents prior to summarization. ATC medication summary statistics are calculated from daily patient totals and rescue medication summary statistics are calculated from average patient uses. Only data from each patient's first study is included here.
Baseline ATC daily dose categories are determined from quartiles.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\Xsscspmedab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.4
Pain Medications at Baseline by Around-the-Clock (ATC) Type by Aberrant Behavior Categories
Safety Analysis Set

Aberrant behavior: None

Type Statistic	Patients Taking Oral Opioids	Patients Taking Transdermal Fentanyl	Patients Taking Intrathecal Medications	Total
ATC medication (mg/day)				
n	564	192	29	756
Mean	208.3	207.5		208.1
SD	209.33	140.80		194.14
SE of mean	8.81	10.16		7.06
Median	120.0	180.0		160.0
Min, max	15.0, 2160.0	60.0, 1440.0		15.0, 2160.0
Rescue medication (mg/BTP)				
n	560	189	28	777
Mean	27.2	31.6	35.7	28.6
SD	28.87	109.35	48.39	59.87
SE of mean	1.22	7.95	9.15	2.15
Median	20.0	20.0	20.0	20.0
Min, max	1.3, 240.0	0.5, 1500.0	5.0, 192.0	0.5, 1500.0
Baseline ATC daily dose (mg), n (%)	564 (100)	192 (100)	29 (100)	785 (100)
<=90	195 (35)	15 (8)	0	210 (27)
>90 - <=160	140 (25)	57 (30)	0	197 (25)
>160 - <=240	104 (18)	88 (46)	0	192 (24)
>240	125 (22)	32 (17)	0	157 (20)
Intrathecal	0	0	29 (100)	29 (4)

Notes: Patients using intrathecal opioids were not summarized in ATC or total since these opioids were not converted to morphine equivalents.
All non-intrathecal doses are converted to oral morphine equivalents prior to summarization. ATC medication summary statistics are calculated from daily patient totals and rescue medication summary statistics are calculated from average patient uses. Only data from each patient's first study is included here.
Baseline ATC daily dose categories are determined from quartiles.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\Xsscspmedab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.5
Aberrant Medical History Drug Predictors by Aberrant Behavior Categories
Safety Analysis Set

Variable Statistic, n (%)	Aberrant Behavior: High Risk (N=30)	Aberrant Behavior: All Aberrant (N=156)	Aberrant Behavior: None (N=785)	Total (N=941)
Anxiety				
Yes	11 (37)	58 (37)	272 (35)	330 (35)
No	19 (63)	98 (63)	513 (65)	611 (65)
Mood				
Yes	16 (53)	78 (50)	438 (56)	516 (55)
No	14 (47)	78 (50)	347 (44)	425 (45)
Psychosis/Mania				
Yes	2 (7)	9 (6)	21 (3)	30 (3)
No	28 (93)	147 (94)	764 (97)	911 (97)
History of abuse				
Yes	0	1 (<1)	12 (2)	13 (1)
No	30 (100)	155 (>99)	773 (98)	928 (99)
Headache				
Yes	8 (27)	56 (36)	248 (32)	304 (32)
No	22 (73)	100 (64)	537 (68)	637 (68)

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsflag1.sas (LJ) Data Extract: 10/25/07 16:25 Table Generation: 10/25/07 16:28

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Age Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=42 yrs	55 (35)	189 (24)	2.5178	(1.5, 4.3)	0.0006
>42 to <=49 yrs	50 (32)	209 (27)	2.0699	(1.2, 3.6)	0.0072
>49 to <=55 yrs	28 (18)	188 (24)	1.2886	(0.7, 2.3)	0.3968
>55 yrs	23 (15)	199 (25)	1.0000	(1.0, 1.0)	

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Race Group	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Black	7 (4)	40 (5)	0.9917	(0.2, 5.0)	0.9911
Other	3 (2)	17 (2)	1.0000	(1.0, 1.0)	
White	146 (94)	728 (93)	1.1364	(0.4, 4.9)	0.8398

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Sex	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Female	82 (53)	452 (58)	0.8164	(0.6, 1.2)	0.2486
Male	74 (47)	333 (42)	1.0000	(1.0, 1.0)	

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

BMI Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=24.80	39 (25)	195 (25)	1.0000	(1.0, 1.0)	
>24.80 - <=29.14	45 (29)	188 (24)	1.1968	(0.7, 1.9)	0.4569
>29.14 - <=34.20	38 (24)	197 (25)	0.9645	(0.6, 1.6)	0.8846
>34.20	33 (21)	198 (25)	0.8333	(0.5, 1.4)	0.4783
Missing	1 (<1)	7 (<1)	0.7143	(0.0, 4.2)	0.7561

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline SF-36 Physical Composite Score Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=22.24	27 (17)	191 (24)	0.6255	(0.4, 1.1)	0.0823
>22.24 - <=26.00	32 (21)	184 (23)	0.7696	(0.5, 1.3)	0.3128
>26.00 - <=31.50	42 (27)	175 (22)	1.0620	(0.7, 1.7)	0.8063
>31.50	40 (26)	177 (23)	1.0000	(1.0, 1.0)	
Missing	15 (10)	58 (7)	1.1444	(0.6, 2.2)	0.6903

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline SF-36 Mental Composite Score Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=34.49	30 (19)	188 (24)	0.9176	(0.5, 1.6)	0.7539
>34.49 - <=40.75	37 (24)	180 (23)	1.1819	(0.7, 2.0)	0.5253
>40.75 - <=51.56	42 (27)	175 (22)	1.3800	(0.8, 2.3)	0.2107
>51.56	32 (21)	184 (23)	1.0000	(1.0, 1.0)	
Missing	15 (10)	58 (7)	1.4871	(0.7, 2.9)	0.2532

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline SF-36 Physical Composite Score by Median	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=26.00	59 (38)	375 (48)	0.6754	(0.5, 1.0)	0.0350
>26.00	82 (53)	352 (45)	1.0000	(1.0, 1.0)	
Missing	15 (10)	58 (7)	1.1102	(0.6, 2.0)	0.7397

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline SF-36 Mental Composite Score by Median	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=40.75	67 (43)	368 (47)	0.8833	(0.6, 1.3)	0.5004
>40.75	74 (47)	359 (46)	1.0000	(1.0, 1.0)	
Missing	15 (10)	58 (7)	1.2547	(0.7, 2.3)	0.4736

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline POMS Total Mood Score Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=6.00	42 (27)	183 (23)	1.0000	(1.0, 1.0)	
>28.00 - <=54.00	36 (23)	183 (23)	0.8571	(0.5, 1.4)	0.5375
>54.00	29 (19)	181 (23)	0.6981	(0.4, 1.2)	0.1721
>6.00 - <=28.00	34 (22)	179 (23)	0.8276	(0.5, 1.4)	0.4555
Missing	15 (10)	59 (8)	1.1077	(0.6, 2.1)	0.7607

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

History of Mood	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
No	78 (50)	347 (44)	1.0000	(1.0, 1.0)	
Yes	78 (50)	438 (56)	0.7922	(0.6, 1.1)	0.1845

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

History of Anxiety	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
No	98 (63)	513 (65)	1.0000	(1.0, 1.0)	
Yes	58 (37)	272 (35)	1.1162	(0.8, 1.6)	0.5454

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

History of Psychosis/Mania	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
No	147 (94)	764 (97)	1.0000	(1.0, 1.0)	
Yes	9 (6)	21 (3)	2.2274	(1.0, 4.8)	0.0499

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

History of Abuse	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
No	155 (>99)	773 (98)	1.0000	(1.0, 1.0)	
Yes	1 (<1)	12 (2)	0.4156	(0.0, 2.1)	0.4006

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

History of Headaches	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
No	100 (64)	537 (68)	1.0000	(1.0, 1.0)	
Yes	56 (36)	248 (32)	1.2126	(0.8, 1.7)	0.2941

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Primary Pain Diagnosis Group	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Back pain	87 (56)	431 (55)	1.0833	(0.7, 1.7)	0.7291
Neuropathic pain	30 (19)	161 (21)	1.0000	(1.0, 1.0)	
Other	39 (25)	193 (25)	1.0845	(0.6, 1.8)	0.7599

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Pathophysiology of the Primary Pain	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Missing/Not collected	16 (10)	90 (11)	0.8624	(0.5, 1.6)	0.6385
Mixed	44 (28)	229 (29)	0.9321	(0.6, 1.5)	0.7594
Predominantly neuropathic	47 (30)	228 (29)	1.0000	(1.0, 1.0)	
Predominantly nociceptive	49 (31)	238 (30)	0.9987	(0.6, 1.6)	0.9955

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.6
Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Baseline ATC Daily Dose Quartiles	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
<=90	36 (23)	210 (27)	4.9714	(1.0, 89.9)	0.1205
>160 - <=240	29 (19)	192 (24)	4.3802	(0.9, 79.5)	0.1541
>240	41 (26)	157 (20)	7.5732	(1.5, 136.8)	0.0498
>90 - <=160	49 (31)	197 (25)	7.2132	(1.5, 130.0)	0.0550
Intrathecal	1 (<1)	29 (4)	1.0000	(1.0, 1.0)	

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk4.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

Ad Hoc Summary RA.7
Final Main Effect Model: Odds Ratio of Aberrant Behaviors by Patient Characteristics
Safety Analysis Set

Patient Characteristic	Category	Any Aberrant (N=156)	None (N=785)	Odds Ratio	95% CI	P-value
Age Quartiles	<=42 yrs	55 (35)	189 (24)	2.3741	(1.4, 4.1)	0.0014
	>42 to <=49 yrs	50 (32)	209 (27)	1.9970	(1.2, 3.5)	0.0113
	>49 to <=55 yrs	28 (18)	188 (24)	1.2604	(0.7, 2.3)	0.4425
	>55 yrs	23 (15)	199 (25)	1.0000	(1.0, 1.0)	
Baseline ATC daily dose quartiles	<=90	36 (23)	210 (27)	4.4619	(0.9, 80.9)	0.1488
	>160 - <=240	29 (19)	192 (24)	4.0681	(0.8, 74.0)	0.1767
	>240	41 (26)	157 (20)	6.4575	(1.3, 117.0)	0.0715
	>90 - <=160	49 (31)	197 (25)	6.7168	(1.4, 121.3)	0.0649
	Intrathecal	1 (<1)	29 (4)	1.0000	(1.0, 1.0)	
History of Psychosis/Mania	No	147 (94)	764 (97)	1.0000	(1.0, 1.0)	
	Yes	9 (6)	21 (3)	1.9203	(0.8, 4.2)	0.1162

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xsscsrisk7.sas (FX) Data Extract: 10/22/07 16:58 Table Generation: 10/25/07 16:29

List of Subject/Patient Data Listings

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_001002	Medication Theft		606
3040_001003	Lost to Follow-up		650
3040_003001	Medication Theft		96
3040_003003	Lost to Follow-up		187
3040_003005	Fear of Addiction		215
3040_003007	Medication Theft		380
3040_003008	Lost to Follow-up		584
	Medication Theft		.
3040_003010	Fear of Addiction		115
3040_003011	Overuse of study medication		433
3040_003013	Overuse of study medication		170
3040_003015	Fear of Addiction		83
3040_003016	Medication Theft		160
3040_003017	Overuse of study medication		127
	Medication Theft		12
3040_003018	Overuse of study medication		438
	Medication Theft		135
3040_003021	Abuse/dependence	YES	55
	Overdose	YES	11
3040_005024	Overuse of study medication		244
	Overuse of study medication		184
3040_007005	Lost to Follow-up		125

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_007006	Seeking prescriptions from other sources		188
3040_008011	Lost to Follow-up		216
3040_008016	Positive UDS	YES	189
3040_009006	Lost to Follow-up		596
3040_009008	Lost to Follow-up		466
3040_009012	Lost to Follow-up		411
3040_009014	Overuse of study medication		333
3040_010006	Lost to Follow-up		68
3040_010007	Lost to Follow-up		413
3040_010016	Lost to Follow-up		74
3040_010018	Overuse of study medication		374
3040_011004	Overuse of study medication		7
3040_011013	Was Discharged from Practice		8
3040_012010	Overuse of study medication Overuse of study medication		305 269
3040_012011	Medication Theft		293
3040_012012	Overuse of study medication		125
3040_012016	Overuse of study medication		334
3040_012021	Lost to Follow-up		220
3040_013008	Positive UDS	YES	390

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_013009	Overuse of study medication		165
	Medication Theft		127
3040_013013	Positive UDS	YES	225
	Medication Theft		128
3040_013017	Lost Study medication		397
3040_013018	Lost to Follow-up		245
	Abuse/dependence	YES	.
3040_013022	Lost to Follow-up		519
3040_013027	Medication Theft		301
3040_013042	Overuse of study medication		522
3040_015001	Lost to Follow-up		460
3040_017003	Overuse of study medication		552
	Overuse of study medication		514
3040_017005	Lost to Follow-up		347
3040_017009	Lost to Follow-up		84
3040_017010	Unapproved use of drug to treat another symptom		378
3040_017014	Positive UDS	YES	410
3040_018006	Medication Theft		458
3040_018011	Overuse of study medication		11
3040_018020	Medication Theft		564
3040_018021	Overuse of study medication		374
	Overuse of study medication		366

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_019001	Positive UDS	YES	519
3040_019002	Positive UDS	YES	519
	Medication Theft		483
	Medication Theft		.
3040_019004	Overdose	YES	345
	Overdose	YES	341
3040_019010	Overdose	YES	490
3040_019014	Overuse of study medication		416
	Overuse of study medication		389
	Medication Theft		225
3040_019022	Medication Theft		121
	Medication Theft		30
3040_021002	Positive UDS	YES	191
3040_022007	Overuse of study medication		190
3040_022009	Overuse of study medication		134
3040_023005	Unreliability		190
3040_024002	Motor Vehicle Accident		99
3040_024020	Overuse of study medication		227
3040_024026	Lost to Follow-up		332
3040_024031	Medication Theft		311
3040_025003	Overdose	YES	131
3040_025005	Was Discharged from Practice		400
3040_025019	Unapproved use of drug to treat another symptom		300

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_025021	Abuse/dependence	YES	.
3040_026003	Overuse of study medication		67
3040_026010	Overdose	YES	107
3040_026015	Overuse of study medication		241
3040_027003	Lost to Follow-up		350
3040_027006	Lost to Follow-up		43
3040_027009	Lost to Follow-up		74
3040_027016	Motor Vehicle Accident		407
3040_027020	Lost to Follow-up		119
3040_027024	Abuse/dependence	YES	106
3040_030003	Medication Theft		141
3040_030008	Overdose	YES	601
3040_030022	Overuse of study medication Overuse of study medication Medication Theft		249 197 29
3040_031007	Medication Theft		.
3040_031014	Medication Theft		92
3040_031015	Lost to Follow-up		148
3040_032012	Overuse of study medication		492
3040_032013	Motor Vehicle Accident		9
3040_033001	Using non-prescribed medication		33

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_033006	Overuse of study medication		225
3040_033010	Aquiring opioids from other medical sources		27
3040_033012	Medication Theft		181
	Overuse of study medication		435
3040_033014	Using non-prescribed medication		43
3040_033020	Overuse of study medication		27
3040_033021	Lost Study medication		83
3040_034005	Overuse of study medication		100
3040_034010	Motor Vehicle Accident		457
3040_034019	Overuse of study medication		63
3040_034037	Unreliability		126
3040_034048	Positive UDS	YES	330
3040_034053	Lost Study medication		338
3040_034065	Overuse of study medication		519
	Medication Theft		505
3040_037002	Medication Theft		556
3040_040002	Overuse of study medication		465
	Overuse of study medication		400
3040_040009	Overuse of study medication		385
	Overuse of study medication		356
3040_040010	Medication Theft		437
	Overuse of study medication		372
	Overuse of study medication		338

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3040_040012	Overuse of study medication		95
3040_041009	Lost to Follow-up		171
3040_042010	Medication Theft		42
3040_042023	Using non-prescribed medication		120
3040_043004	Medication Theft		420
3040_043011	Medication Theft		34
3041_403001	Lost to Follow-up		127
3041_408007	Medication Theft		243
3041_410001	Lost to Follow-up		31
3041_411002	Lost to Follow-up		168
3041_411005	Lost to Follow-up		445
3041_412002	Overuse of study medication		85
3041_412004	Abuse/dependence	YES	63
3041_413001	Fear of Addiction		106
3041_418002	Overuse of study medication		463
	Overuse of study medication		425
3041_418005	Overuse of study medication		403
	Overuse of study medication		386
	Overuse of study medication		368
	Overuse of study medication		237
3041_418010	Medication Theft		271
3041_418012	Lost Study medication		404

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3041_418012	Overuse of study medication		404
3041_424006	Overuse of study medication		392
3041_424007	Abuse/dependence	YES	64
3041_425006	Positive UDS	YES	309
3041_432004	Positive UDS	YES	262
3041_432006	Using non-prescribed medication		304
3041_432008	Medication Theft		34
3042_503003	Overdose	YES	6
3042_505004	Fear of Addiction		24
3042_505005	Overuse of study medication		30
3042_506003	Medication Theft		60
3042_508002	Lost to Follow-up		466
3042_511003	Overdose	YES	298
3042_512003	Lost to Follow-up		64
3042_512004	Abuse/dependence	YES	144
3042_513006	Positive UDS	YES	197
3042_513007	Lost to Follow-up		.
3042_513017	Overdose	YES	71
3042_513021	Medication Theft		194
3042_518001	Overuse of study medication		397

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

Subject ID	Aberrant Behavior Category	High Risk Flag	Study Day^
3042_518002	Fear of Addiction		27
3042_518004	Lost Study medication		146
3042_525002	Lost to Follow-up		73
3042_525004	Overuse of study medication		135
3052_001010	Overuse of study medication		44
3052_001011	Lost to Follow-up		64
3052_001012	Overuse of study medication		25
3052_002003	Abuse/dependence	YES	.
3052_002008	Medication Theft		11
3052_002009	Medication Theft		.
3052_002021	Lost to Follow-up		116
3052_003009	Positive UDS	YES	1
3052_024003	Positive UDS	YES	-24
3052_026008	Overdose	YES	99

^Study Day: Day relative to the overall start of treatment.

Source: q:\biostats\c25608\scs_07\cpstats\pgms\xlscsab.sas (LJ) Data Extract: 10/25/07 16:24 Table Generation: 10/25/07 16:34

Ad Hoc Listing RA.1
Aberrant Behavior Categories
Enrolled Patients

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Total number of Patients: 157

APPENDIX C
STUDY DRUG THEFT

Study Drug Theft
(Enrolled Patients)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040							
001002	14 December 2006	606	7 (600 mcg)	Report filed. Copy at center.	No	No	Patient's pocket book (containing study medication) was stolen at a Pharmacy.
003001	18 July 2005	96	Unknown (800 mcg)	No report filed.	No	No	Patient said that study drug had been taken by a young man while the patient was on vacation. Following a phone call to the mother of the young man, the stolen study drug was returned. It was unclear if any study drug was missing.
003007	6 July 2006	380	Unknown (800 mcg)	No report filed	No	No	Patient said that study drug was stolen from his property during an overnight stay at the Salvation Army.
003008	NAV	NAV	18 (800 mcg)	No report filed	No	No	Patient said she was pulled over by a police officer whilst driving; the police officer took the study drug because he did not believe that she was participating in a clinical trial. The patient was eventually withdrawn from the study on day 584 because she was lost to follow-up.
003016	11 January 2006	160	22 (600 mcg)	No report filed	Yes	No	Patient said that her son used the missing study drug.

Footnotes and abbreviations are provided at the end of the table. (continued)

Study Drug Theft
(Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
003017	21 August 2005	12	60 (600 mcg)	Report filed. No copy at center	No	No	Patient said that study drug was stolen from his car while it was parked outside a store. The patient was eventually withdrawn from the study on day 127 due to noncompliance with study drug.
003018	7 January 2006	135	66 (800 mcg)	Report filed. No copy at center	No	No	Patient said that his truck was broken into and study drug was stolen along with other personal property. The patient was eventually withdrawn from the study on day 438 due to noncompliance with study drug.
012011	12 June 2006	293	Unknown	Report filed. Copy at center.	No	No	Patient said that her purse containing study drug was stolen from her workplace.
013009	23 September 2005	127	59[b] (800 mcg)	Report filed. No copy at center	No	No	Patient said that study drug was stolen from their car which was left unlocked and unattended for a few moments at the car wash. The patient was eventually withdrawn from the study on day 165 due to noncompliance with study drug.

Footnotes and abbreviations are provided at the end of the table.

(continued)

Study Drug Theft
(Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
013013	18 October 2005	128	79 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from her open car while she was rearranging items in the car. The patient was eventually withdrawn from the study due to a positive UDS (amphetamine/methamphetamine) on day 198 (protocol violation).
013027	25 May 2006	301	77 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from her unlocked car (car locks were broken) when she was at the grocery store or gas station.
018006	5 August 2006	458	12 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug and other property were stolen from a locked cabinet in her house during a 20th wedding anniversary party.
018020	9 December 2006	564	75[b] (800 mcg)	Report filed. Copy at center.	No	No	Patient said that she inadvertently left her bag containing study drug on the ground of the parking lot where her grandmother lives. When she returned to pick up the purse the study drug was missing.

Footnotes and abbreviations are provided at the end of the table.

(continued)

Study Drug Theft
(Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
019002	NAV	NAV	6 (800 mcg)	No report filed.	No	No	Patient said that study drug was stolen from her bag while she was out of town. The patient was eventually withdrawn from the study on day 519 due to a positive UDS for cocaine (protocol violation).
	28 August 2006	483	24 (800 mcg)	No report filed.	No	No	Patient said that study drug was stolen from her checked baggage during an airline flight.
019014	24 January 2006	225	18 (800 mcg)	No report filed.	No	No	Patient said that his carry-on bag was removed from an airplane and placed in the cargo hold. The bag containing his study drug was stolen.
019022	14 September 2006	121	72 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study medication was stolen from his car along with other property while his car was at an auto repair shop.
	15 June 2006	30	Unknown (800 mcg)	No report filed	No	No	Patient said that baggage containing study drug was lost at the airport.

Footnotes and abbreviations are provided at the end of the table.

(continued)

Study Drug Theft
(Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
024031	6 April 2006	311	12[b] (800 mcg)	Report filed. Copy at center.	No	Yes	Patient's husband found dead following a suspected overdose of study drug. Between 12 and 18 tablets of study drug were missing.[c]
030003	6 September 2005	141	Unknown (Unknown)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from his home after he was taken to the hospital by ambulance; the doors to his house were accidentally left open.
030022	12 June 2006	29	12 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from her home by a friend who was a recovering drug addict.
031007	NAV	NAV	16 (600 mcg)	No report filed.	No	No	Patient suspected that friends of her nephew had stolen study drug from her house while she was out.
031014	7 November 2005	92	66 (800 mcg)	Report filed. Copy at center.	No	No	Patient suspects that guests at his home stole study drug; patient was not acquainted with the guests.
033012	11 January 2006	181	6 (800 mcg)	No report filed.	No	No	Patient said that study drug was stolen from workplace. . The patient was eventually withdrawn from the study on day 461 due to noncompliance with study drug.

Footnotes and abbreviations are provided at the end of the table.

(continued)

Study Drug Theft
(Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
034065	8 January 2007	505	75 (800 mcg)	No report filed.	No	No	Patient said that his bag containing study drug was stolen from a hotel room. The patient was eventually withdrawn from the study on day 519 due to noncompliance with study drug.
037002	22 December 2006	556	26 (400 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from his motel room while he left the room.
040010	22 February 2007	437	12 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from her home by her tenant.
042010	1 February 2006	42	102 (400 mcg)	No report filed.	Yes	Yes	Patient said that study drug had been stolen by a nurse at the in-patient unit.
043004	11 December 2006	420	36 (800 mcg)	No report filed	No	No	Patient said that study drug was missing from his checked baggage following an airplane flight.
043011	29 January 2006	34	41 (600 mcg)	No report filed	Yes	Yes	Patient said that study drug was stolen by his girlfriend.
408007	25 December 2006	215	36 (600 mcg)	No report filed.	No	No	Police were notified but no report filed.
418010	23 September 2006	255	57 (800 mcg)	Report filed. Copy at center.	No	No	Patient said that study drug was stolen from her bedroom in her house while she was absent all day.

Footnotes and abbreviations are provided at the end of the table.

(continued)

Study Drug Theft (Enrolled Patients) (Continued)

Study Patient	Theft date	Day relative to start of study drug administration	Quantity (dose) stolen[a]	Police report	Stolen by person with opportunity and regular access to study drug (yes/no)	Patient withdrawn following theft (yes/no)	Comments
Study 3040 (continued)							
432008	7 January 2006	19	102 (800 mcg)	Report filed. No copy at center.	Yes	No	Patient's family said that they believed the patient had been assaulted by her husband and her study drug had been stolen.
506003	15 January 2006	34	28 (800 mcg)	Report filed. Copy at center.	Yes	Yes	Patient said that study drug had been stolen from his wife's workplace (where he stored the study drug).
513021	7 August 2006	183	50[b] (800 mcg)	Report filed. No copy at center.	No	No	Patient suspects that cleaner stole study drug; cleaner was not well known to the patient.
Study 3052							
002008	30 October 2006	11	125[b] (800 mcg)	Report filed. Copy at center.	No	Yes	Patient said that study drug, the electronic study diary, and all of his personal belongings were stolen from his apartment.
002009	November 2006	NAV	22 (800 mcg)	Report filed. No copy at center.	No	No	Patient said that study drug was stolen by his boarder. He evicted the boarder and allowed no other boarders until he completed the study.

SOURCE: Clinical study reports for study 3040 and study 3052, and data on file at Cephalon.
[a] Quantity and dose as per information received from patient.
[b] Approximate number.
[c] The husband of patient 024031, who had been participating in study 3040, was found dead on 4 April 2006. This death was considered by the investigator to be possibly related to an overdose of study drug. The patient informed the investigator that she believed her husband took her study drug (800-mcg tablets), as 12 to 18 tablets were missing (data on file).
NAV=not available; UDS=urine drug screen.