CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022510Orig1s000

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	January 7, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	022510
Applicant Name	ProStrakan
Date of Submission	August 5, 2009
PDUFA Goal Date	June 4, 2010/September 5, 2010 with clock extension
Proprietary Name / Established (USAN) Name	ABSTRAL/ Fentanyl sublingual tablets
Dosage Forms / Strength	Sublingual tablets 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg
Proposed Indication	For the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	Frank Pucino, Pharm.D., M.P.H.
Statistical Review	Yan Zhou, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Muthukumar Ramaswamy, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Zhihong Li, Ph.D.; Suresh Doddapaneni, Ph.D.
DSI	Susan Leibenhaut, M.D.; Tejashri Purohit-Sheth, M.D., Jean Mulinde, M.D.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Lori Cantin, R.Ph.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Steve L. Morin, R.N., B.S.N.; Gita A. Toyserkani, Pharm.D.; Megan Moncur, M.S.; Jeanne Perla, Ph.D.; Claudia Karwoski, Pharm. D., Cynthia LaCivita, Pharm.D., Marcia Britt-Williams, Ph.D., Sharon Mills, B.S.N., R.N., CCRP, Stephen Sun, M.D.
DDMAC	Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
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OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DDMAC=Division of Drug Marketing, Advertising and Communications

1. Introduction

ABSTRAL is a sublingual tablet containing fentanyl as the active pharmaceutical ingredient. ProStrakan Inc. has submitted this application to support approval of the following indication: for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain. There are three transmucosal fentanyl products already approved for this indication: Actiq, a lozenge on a stick approved in 1998; Fentora, a buccal tablet approved in 2006; and Onsolis, a buccal soluble film approved in 2009. As with the Fentora and Onsolis applications, this is a 505(b)(2) application referencing NDA 020747 for Actiq, and the evidentiary basis for a finding of efficacy for ABSTRAL is a single, adequate and well-controlled clinical trial of a design based on the original studies performed for Actiq. The major regulatory concern related to this application has been the development of an adequate Risk Evaluation and Mitigation Strategy (REMS). Based on the potential for development of additional immediate-release fentanyl products that could be intended for transmucosal absorption in areas other than the mouth, the Agency has

designated this class of opioid drug products Transmucosal Immediate-Release Fentanyl products, or TIRFs.

2. Background

Fentanyl is an extremely potent opioid that has the potential to cause serious morbidity and death due to respiratory failure if administered to a non-opioid tolerant person. It is also a highly sought after drug of abuse and sells for a high price on the street when either legitimate product is diverted or illicit product, known as China White, becomes available.

This application represents the fourth NDA for an oral transmucosal fentanyl formulation. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due to the similarity in its appearance to a lollipop. A Risk Management Plan (later defined as a RiskMAP) was created to attempt to manage some of the risk associated with this product. In addition to identifying the risk for accidental pediatric exposure and providing some methods to try and minimize that risk, other goals described in the RiskMAP included preventing use in opioid non-tolerant patients and other off-label uses. The only clearly unique adverse event associated with Actiq in post-marketing experience has been the occurrence of dental caries, related to the sugar content in the Actiq lozenge.

Fentora was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. The only adverse event associated with Fentora that differed from Actiq in pre- and post-marketing experience was the occurrence of local ulcers in the mouth at the site of drug exposure. Fentora was approved with a RiskMAP comparable to Actiq. Actiq and Fentora were approved for the same indication sought by the applicant, the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The intended population is already on around-the-clock opioids for pain and has episodes of pain that stand out from their background pain. This indication reflects the need for a specific treatment to meet the needs of cancer patients with breakthrough pain, characterized by a relatively early onset of action, relatively short duration of action and high analgesic potency. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patients to be opioid tolerant, a physiological state in which patients are able to tolerate higher opioid doses without experiencing the CNS and respiratory depression associated with these drugs.

Based on the post-marketing history of Actiq, it has become clear that prescribers have found Actiq to be useful in patients without cancer pain, both in the settings of chronic non-cancer pain with episodes of breakthrough pain and other chronic painful conditions not generally associated with breakthrough pain episodes. Of note, use of the term breakthrough pain in non-cancer pain is somewhat controversial. In the Actiq RiskMAP

quarterly reports, the use of Actiq in non-cancer pain has exceeded its use in cancer pain, although it is used primarily in opioid tolerant patients with chronic non-cancer pain.

Fentora has greater bioavailability than Actiq and the formulation is less easily removed from the mouth once dosing has begun. Efforts were made to make the difference in bioavailability clear in the Fentora labeling with specific statements that patients should not be converted from Actiq on a mcg for mcg basis and that Fentora is not a generic version of Actiq. However, post-marketing reports have demonstrated a variety of medication errors that include direct conversion on a mcg for mcg basis by prescribers and product substitution at the pharmacy level, in addition to incorrect dosing instructions. The quarterly RiskMAP reports document the very disturbing trend of a steadily increasing frequency of use in patients who are not opioid tolerant. In the first year of marketing there were two deaths reported in patients prescribed Fentora for headache.

As a result of the post-marketing information from Actiq and Fentora, it appeared that the RiskMAP in place for Actiq and Fentora was not effective in mitigating the risks of these products. During a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees on May 6, 2008, the committee members heard presentations from the FDA, SAMHSA and Cephalon, the NDA holder for Actiq and Fentora, about the risks associated with Fentora and the failure of the RiskMAP to mitigate those risks. The committee recommended a more comprehensive program that included patient and physician registration and improved risk communication.

Onsolis, the third transmucosal fentanyl product, was approved with a REMS, as authorized under the Food and Drugs Amendments Act passed in September of 2007. The Onsolis REMS, known as FOCUS (Full Ongoing Commitment to User Safety) calls for dispensing Onsolis via specialty pharmacies. The specialty pharmacies ship Onsolis by traceable courier to enrolled patients only after all of the following criteria have been met:

1) Patients have been enrolled in the program, based on a valid prescription from an active prescriber
2) Patients or legally authorized representatives have been counseled regarding the importance of being on an around-the-clock opioid regimen for an adequate amount of time to ensure that they are opioid tolerant and on appropriate Onsolis product use
3) The FOCUS pharmacy has verified that the prescriber and the patient are both enrolled, that the patient has received a FOCUS program counseling call to review the safe use conditions, and that the prescriber has counseled the patient

An additional component of the FOCUS program is a plan to re-counsel and re-enroll prescribers, patients and pharmacies when substantial changes are made to the program or at an interval of at least every two years. If an enrolled patient transfers to another prescriber, the patient and new prescriber must complete a new FOCUS program patient enrollment form. There is also a distribution and prescription data monitoring plan. Finally, the plan requires that each FOCUS pharmacy keep a record of delays in patients receiving the drug of greater than 72 hours from the time the prescription was received by

the pharmacy. The reasons for the delays are to be investigated and reviewed monthly. There has been limited prescribing of Onsolis since its approval, therefore it is not possible at this time to assess the impact of the FOCUS program on safe use of the product.

ProStrakan submitted their proposed REMS with their application. In October of 2010, the Agency requested that all TIRFs should have a single, shared REMS in order to minimize the burden to healthcare providers and patients. A REMS Notification Letter was sent to all innovator and generic TIRF product sponsors, including ProStrakan, informing them that the elements of a single, shared REMS that could be implemented across their programs. As the shared REMS will take substantial time to develop, the individual sponsors were instructed to develop and implement individual TIRF REMS within six months of receiving the notification letter. These individual REMS would still be required to include the same general elements of the eventual shared REMS.

ProStrakan has submitted their revised REMS in response to the Division's REMS Notification Letter. The details of their REMS are discussed below in Section 13. After multiple discussions regarding this revised REMS, the review team and the applicant have reached agreement on a final REMS that includes most of the same elements as the FOCUS program, but differs in a few substantial ways that I will note below.

3. CMC

The ABSTRAL tablets are packaged in child resistant blister cards and are distinguished by debossing of the first number of the strength and by their different shapes. Due to the low dose of fentanyl in these tablets, the manufacturer included Design of Experiments studies which examined the effect of blending parameters on the final drug product characteristics. They then identified critical unit operations, process parameters, in-process controls and product characteristics for the finished product.

There are no novel excipients. The drug product specifications, including content uniformity, were found to be adequate and conform to ICH guidances. Adequate stability data was provided to assign a shelf-life of 36 months.

(b) (4)

Abstral (fentanyl) sublingual tablets are manufactured at Novartis, Lincoln, NE, USA.

The facilities review and inspection were found to be acceptable. I concur with the review team that no additional CMC requirements are necessary for approval of the ABSTRAL NDA.

4. Nonclinical Pharmacology/Toxicology

The applicant performed a single-dose oral toxicology study in dogs and 4- and 28-day toxicology studies in guinea pigs and hamsters. Although the guinea pig study was not

performed as a GLP study, Dr. Bolan has concluded that ABSTRAL appears to have a relatively low potential for toxicity to the oral mucosa.

I concur with the review team that no additional nonclinical pharmacology or toxicology data are necessary for approval of the ABSTRAL NDA.

5. Clinical Pharmacology/Biopharmaceutics

The following is a summary of the clinical pharmacology and biopharmaceutics data submitted in this application reproduced from pages 6 and 7 of Dr. Shibuya's review:

> ProStrakan proposes to market strengths of 100, 200, 300, 400, 600, and 800 mcg. Obviously, during dose-finding, it is not practical to prescribe and dispense all strengths. Thus, a focus of the Applicant's Clinical Pharmacology program has been to determine whether multiples of lower strengths may be used during dose titration. Along with establishing single- and multiple-dose pharmacokinetics and dose proportionality, the other key issues that were explored in the Clinical Pharmacology program have been whether drug product manufactured at different sites behaves similarly and the relative bioavailability to Actiq, the Reference Drug. Table 1, summarizes the key Clinical Pharmacology studies and findings…

Table 1: Summary of key Clinical Pharmacology Studies (a total of 13 studies were submitted)

Study #	Objective	Results	Comments
EN3267-010	Comparison of 400 mcg strength manufactured at Orexo vs. Novartis	Products from manufacturing sites are bioequivalent	
EN3267-003	Comparison of one x 800 mcg; two x 400 mcg; four x 200 mcg	All dose regimens produced equivalent Cmax and AUC	
2246-EU-005	Dose proportionality from 100 to 800 mcg	The product is dose proportional.	
EN3267-001	Relative bioavailability to Actiq	The bioavailability of ABSTRAL is approximately twice that of Actiq.	Study was not conducted correctly. The Actiq was discarded after 15 minutes regardless of the amount remaining.
EN3267-012	Relative bioavailability to Actiq (ABSTRAL 800 mcg vs. Actiq 1600 mcg)	Adjusted for dose, ABSTRAL is bioequivalent to Actiq	
EN3267-013	Relative bioavailability to Actiq (both products tested at 800 and 1600 mcg)	ABSTRAL is bioequivalent to Actiq	

Key pharmacokinetic parameters follow in Table 2 from Study 2246-EU-005, a single- and multiple-dose pharmacokinetic study in healthy Japanese subjects.

Table 2: Summary of Key Pharmacokinetic Indices

Pharmacokinetic Parameter [a]	Dose of Fentanyl (µg)							
	n	100 µg	n	200 µg	n	400 µg	n	800 µg[b]
T_{first} (hours)	12	0.25 (0.24-0.41)	12	0.25 (0.10-0.27)	12	0.25 (0.08-0.25)	12	0.08 (0.08-0.25)
T_{max} (hours)	12	0.50 (0.31-2.00)	12	0.87 (0.27-4.00)	12	1.00 (0.50-1.99)	12	0.50 (0.25-1.00)
C_{max} (ng/mL)	12	0.187 (0.0611)	12	0.302 (0.0923)	12	0.765 (0.288)	12	1.42 (0.466)
C_{6h} (ng/mL)	12	0.0432 (0.0128)	12	0.0833 (0.0305)	12	0.206 (0.0848)	12	0.395 (0.206)
AUC_{τ} (hour*ng/mL)	12	0.599 (0.142)	12	1.06 (0.196)	12	2.60 (0.811)	12	4.49 (1.44)
AUC_{0-t} (hour*ng/mL)	12	0.778 (0.266)	12	1.68 (0.49)	12	4.97 (1.88)	12	8.48 (2.88)
AUC_{0-inf} (hour*ng/mL)	12	0.974 (0.332)	12	1.92 (0.525)	12	5.49 (1.93)	12	8.95 (2.97)
$T_{1/2}$ (hours)	12	5.02 (2.58)	12	6.67 (2.01)	12	13.5 (5.03)	12	10.1 (3.42)
Cl/F (L/hour)	12	113 (35.7)	12	112 (31.5)	12	82.9 (32.1)	12	101 (38.8)

Source: Clinical Study Report, 2246-EU-005, page 78/1179

Drs. Li and Doddapaneni are recommending approval from the clinical pharmacology perspective for this product.

I concur with the review team that no additional clinical pharmacology or biopharmaceutics data are required for approval of the ABSTRAL application.

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

Study EN3267-005 (Study 005) was submitted in support of the efficacy of ABSTRAL. According to the standard design for products of this class, eligible subjects were first enrolled into an open-label, dose-finding period. The subjects were initially treated with 100 mcg doses of ABSTRAL for each episode of breakthrough pain. The doses were titrated up for inadequate analgesia. Subjects who were unable to tolerate doses adequate to provide analgesia, and those who were able to tolerate the drug but who did not find adequate relief of their breakthrough pain even at the 800 mcg dose level were discontinued from the study. When a dose did provide adequate analgesia and was considered tolerable it was repeated for the next episode of breakthrough pain. If

tolerability and effective pain relief continued for two consecutive days the subject entered the double-blind period of the study, remaining on this dose.

Subjects continued into the double-blind period of the study were dispensed ten doses numbered from 1 to 10, seven of which were study drug and three of which were placebo. The placebo doses were randomly assigned within the possible ten dose positions. Subjects then self administered the ten doses, in numerical order, for each ensuing episode of breakthrough pain. The dosing interval for both periods of the study was to be no less than 2 hours from the previous dose.

Subjects assessed their pain on an 11-point numerical rating scale captured pre-dose and at 10, 15, 30 and 60 minutes post-dose. The primary efficacy endpoint was the summed pain intensity difference from pre-dose to 30 minutes post-dose, the SPID30. An interim analysis was performed at approximately 75% of the planned enrollment for the double-blind treatment phase which demonstrated a statistically significant treatment effect and no additional subjects were entered into the double-blind period of the study from that time forward.

From page 8 of Dr. Shibuya's review:

> The statistics team noted that the design might not be balanced with regard to the episodes or period and requested that the Applicant submit analyses of the SPID30 including a fixed effect for episode in the ANOVA model. Dr. Zhou also analyzed the SPID30 with fixed effects for treatment, episode, pooled center, sequence, and a random effect patient. To address the potential of confounding due to the unbalanced treatment allocation scheme, the statistical team requested a permutation test.

The following table, reproduced from page 9 of Dr. Shibuya's review summarizes the results of Dr. Zhou's primary efficacy analysis:

Table 2: Study 005, FDA's Primary Efficacy Analysis

SPID30_reviewer	Abstral Sublingual Tablets (N of subjects = 64) (N of episodes = 414)	Placebo (N of subjects = 64) (N of episodes = 177)
LSMEANS (SE)	52 (4)	36 (4)
Difference from Placebo 95% CI	16 (10, 22)	
 P-value*	 < 0.0001	

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence, pooled center and a random effect patient

Source: Dr. Zhou's review, page 9/16

The secondary efficacy endpoint analyses were generally consistent with and supportive of the primary efficacy analysis and are discussed in more detail in Dr. Pucino's review.

Study SuF-002 was a randomized, double-blind trial of one dose each of 100, 200 and 400 mg of ABSTRAL and placebo in opioid-tolerant cancer patients with breakthrough pain. Only 23 subjects completed the study, but the results were supportive of Study 005.

8. Safety

A total of 694 subjects were exposed to ABSTRAL in the clinical development program. Of these, 383 were healthy volunteers and 311 were patients with cancer. As per Drs. Shibuya and Pucino, the assessment of safety in this application was challenging due to the patient population which consisted of generally quite ill cancer patients who were already on around the clock opioids. Nevertheless, I concur with the review team that there were no unusual or unexpected safety findings.

There were 29 deaths, all in cancer patients. Dr. Pucino has done a thorough analysis of these deaths and has included narratives and discussions for each individual case in his review. Based on these narratives and Dr. Pucino's discussions and conclusions, I concur with him and Dr. Shibuya that these deaths were unlikely to have been directly related to study drug exposure alone, but rather were probably related to progression of the underlying disease and/or concomitant treatments. However, some of the adverse events leading up to these deaths may have been exacerbated by exposure to study drug. This is not inconsistent with the clinical setting. The use of a high-dose, high-potency opioid in an extremely ill cancer patient may contribute to the patient's death to some degree; but this fact does not lessen the importance of their use in providing relief from the often severe, sometimes intolerable pain suffered by these patients.

The serious, non-fatal adverse events and adverse events leading to discontinuation were also more than likely due to the patients' underlying disease or concomitant treatments. The common adverse events were entirely consistent with the patients' underlying diseases, concomitant treatments or exposure to opioids. Most of the adverse events involving the mouth appeared to be related to the patients' cancer or concomitant treatments, e.g., stomatitis, mucositis. A small number of mild and self-limited events such as mucosal blistering may well have been related to use of the study drug.

9. Advisory Committee Meeting

The review team determined that an advisory committee meeting was unnecessary for this new formulation of fentanyl as there were no unusual issues related to its safety or efficacy compared to the previously approved products in the class, and there were no product concerns that would require the advice of non-Agency experts.

10. Pediatrics

Dr. Shibuya's review notes the following:

> The Applicant requested a waiver for the Pediatric Research Equity Act for patients age 2 years and below because the number of patients available for study is too small. Because the efficacy of opioids may be extrapolated from efficacy in adults, efficacy will not have to be demonstrated in pediatric patients age 3-16 years. However, the Applicant will have to complete a safety and pharmacokinetic study to inform dosing.

However, we now consider the number of pediatric patients under the age of 7 who have chronic pain and are opioid-tolerant to be too small to be feasible to study. Thus, the current required pediatric study for a product with this indication would be a safety and pharmacokinetic study in opioid-tolerant pediatric patients age 7 years to 16 years.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

There are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  This application for ABSTRAL is the fourth for a TIRF product. The applicant has provided adequate data to support the safety and efficacy of the product, and they have provided a REMS which we have concluded meets the criteria outlined to the TIRF manufacturers in the Agency's recent REMS Notification Letter. ProStrakan is actively engaged with the other TIRF manufacturers in the development of a single, shared REMS program. While that program is under development, the overall risk-benefit profile of ABSTRAL is essentially equivalent to the other TIRFs, and this application is approvable with the company's current "interim" REMS.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

  The following summary of the goals of the Abstral REMS has been reproduced from page 4 of the REMS Review Team's review:

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

- Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients;
- Preventing inappropriate conversion between fentanyl products;
- Preventing accidental exposure to children and others for whom it was not prescribed;
- Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

The elements of REMS include:

- A Medication Guide
- Elements to Assure Safe Use (ETASU) including:
  - Healthcare providers who prescribe Abstral for outpatient use will be specifically certified.
  - Pharmacies that dispense Abstral will be specifically certified.
  - Abstral will only be dispensed to patients for outpatient use with documentation of safe-use conditions.
- Implementation System
- Timetable for Submission of Assessments

There are numerous details of the ETASU that have been reviewed and agreed upon by the REMS Review Team. The specific details are discussed in that team's review. The final approved REMS and all relevant REMS materials will be attached to the approval letter. Of note, however, the differences between the Onsolis FOCUS REMS program and the Abstral REMS program are worth mentioning and include:

1) In the FOCUS program, the prescriber enrolls the patient. In the Abstral program, the patient is "passively" enrolled by the pharmacy when they fill their first prescription.
2) In the FOCUS program, the product is only available through specialty pharmacies. In the Abstral program, the product is available to any pharmacy that meets the REMS requirements.
3) In the approved FOCUS program, there is no provision for use of the product in an inpatient setting. The Abstral program allows inpatient pharmacies as well as outpatient pharmacies to become certified; the requirements are slightly different.
4) Regarding the "safe use conditions:"
   a. Both programs require the pharmacy to verify prescriber and patient enrollment prior to dispensing the product. In the FOCUS program this is done by reviewing the REMS database. In the Abstral program, this is done passively via the normal pharmacy workflow and pharmacy management systems.
   b. In the FOCUS program, the Call Center is required to contact the patient with the initial prescription and provide scripted counseling. This must be verified to have occurred before the product can be shipped. In the Abstral

program, the certified pharmacy is encouraged to counsel the patient but there is no required documentation of counseling.

c. In the FOCUS program, patient enrollment includes patient acknowledgement which must be signed and received by the program and verified by the pharmacy before the first prescription can be dispensed. In the Abstral program, the prescriber has 10 working days to submit the physician-patient agreement to the program, so the first prescription can be dispensed without verification that this has been signed by the patient.

5) In the FOCUS program, a knowledge assessment is required of the prescriber but not for the certified specialty pharmacy. In the Abstral program a knowledge assessment is required for both the prescriber and pharmacy.

While these differences are notable, the ultimate objectives of risk management for these products have been determined to be adequately achieved with either of these REMS. However, the long-range plan, as noted above, is to have all TIRF NDA and ANDA holders create and participate in a single, shared REMS. When that program is available, the currently approved REMS will be amended to comply with the shared program.

- Post-Marketing Requirement (PMR)

  A deferred pediatric study in patients ages 7-16 years of age entitled, "A safety and pharmacokinetic study of sublingual fentanyl tablets (ABSTRAL) for the treatment of breakthrough pain, including cancer pain and pain due to chronic medical conditions, in opioid-tolerant children."

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/s/

BOB A RAPPAPORT
01/07/2011