2 SYNOPSIS

Name of Sponsor/Company: Cephalon France	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Fentanyl buccal tablets		
Name of Active Ingredient: Fentanyl citrate (CEP-25608)	**Volume:** **Reference:**	

Title of Study: A European Multicenter Open-Label Study of Breakthrough Cancer Pain: Assessment of Fentanyl Buccal Tablets Titration and Treatment in Opioid Tolerant Patients

Investigators and Study Centers: The study was performed (ie, patients screened) at 135 centers in 7 European countries; France (22 centers), Germany (32 centers), Spain (28 centers), Ireland (2 centers), Italy (26 centers), Poland (18 centers), and UK (7 centers). A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 07 January 2009 to 17 May 2011 **Phase of Development:** IV/IIIb

Primary Objective: The primary objective of the study was to compare the percentage of patients reaching an effective fentanyl buccal tablet (FBT) dose with a starting dose of 100 mcg (group A) to those with a starting dose of 200 mcg (group B).

Secondary Objectives: The secondary objectives of the study were the following:

- to evaluate the safety and tolerability of FBT treatment for breakthrough pain (BTP) based on the assessment of adverse events, vital signs, and concomitant medication usage, and oral mucosal and physical examinations (as part of the risk minimization strategy, special attention was directed to the analysis of reasons for patient withdrawals to assess potential cases of misuse as well as for patients under fentanyl based maintenance therapy)
- to evaluate the analgesic efficacy of FBT treatment for BTP and the proportion of episodes in which standard rescue medication, after the administration of study drug, was required for relief of BTP
- to evaluate the effect of FBT treatment on the patients' quality of life and functional status
- to evaluate the patient's global assessment of FBT treatment for BTP
- to assess long-term safety (when applicable)

Number of Patients (Planned and Analyzed): Approximately 880 patients were planned to be enrolled; 442 patients were screened and 330 patients were enrolled in the open-label titration period. From the 330 patients enrolled and randomized, 312 patients received at least 1 dose of study drug in the titration period (145 patients in the 100 mcg titration group [group A] and 167 patients in the 200 mcg titration group [group B]) and were evaluated for safety and primary efficacy in the titration safety (TSAF) analysis set. Two hundred and twenty-three (223) patients received at least 1 dose of study drug in the treatment period and were evaluated for safety and secondary efficacy in the safety (SAF) analysis set. Eighty-seven (87) patients from the 88 patients eligible for the open-label continuation period received at least 1 dose of study drug in the continuation period and were evaluated for safety in the continuation safety (CSAF) analysis set.

Diagnosis and Main Criteria for Inclusion: Patients were included in the study if all of the following main criteria were met (not all inclusive):

- The patient was willing to provide written informed consent to participate in this study
- The patient was at least 18 years of age
- The patient had a histologically documented diagnosis of cancer (ie, a solid tumor or hematologic malignancy)

- The patient had stable background pain due to cancer
- The patient experienced up to 4 BTP episodes per 24 hours (on average) occurring at the location of the chronic pain, while taking opioid maintenance therapy
- As opioid maintenance therapy, the patient was currently taking 1 of the following: at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone/day, at least 8 mg of hydromorphone/day, of an equianalgesic dose of another opioid for a week or longer before administration of the first dose of study drug

Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The patient was without opioid maintenance therapy, as there was an increased risk of respiratory depression
- The patient had uncontrolled or rapidly escalating pain as determined by the investigator (ie, the opioid maintenance therapy was expected to change between the first and last treatments with study drug), or had pain uncontrolled by therapy that could adversely impact the safety of the patient or that could be compromised by treatment with study drug
- The patient had respiratory depression or chronic obstructive pulmonary disease, or any other medical condition predisposing to respiratory depression

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: FBTs were self-administered by the patients via the oral mucosa. During the open-label dose titration period, patients used 1 to 4 tablets of the 100 mcg or 200 mcg strength to individually titrate upwards to an effective dose through the range of available strengths (ie, 100, 200, 400, 600, or 800 mcg). For the open-label treatment and continuation periods, single dose tablets at the effective dose identified during the titration period were used. The maximum dose allowed per BTP episode was 800 mcg. On any single day, patients were not to use FBT for more than 4 BTP episodes. Patients were instructed to wait at least 4 hours before treating another BTP episode with FBT.

The following batch numbers of FBT were used in this study: 100 mcg (C00035; C02121; C16684; P229943), 200 mcg (C00019; C00020; C00753; C16682; C16683; P230103), 400 mcg (C00021; C00023; C00754; C22272), 600 mcg (C00027; C02966; C02967; C56574), and 800 mcg (C00030; C02969; C02971; C28493; C46135).

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable.

Method of Blinding: This was an open-label study with no blinding. The titration period was randomized and open-label. Patients were randomly assigned to receive treatment with a starting dose of 100 mcg or 200 mcg FBT. The randomization lists were generated for each country at a ratio of 1:1. The treatment and continuation periods were non-randomized and open-label.

Duration of Treatment: Following a 7-day screening period patients entered the open-label titration period. The length of the open-label titration period depended on how long was needed to obtain the effective FBT dose (maximum of 7 days). Patients who reached an effective dose entered the open-label treatment period. The length of the open-label treatment period depended on how long was needed to treat up to 8 episodes of BTP with FBT (maximum of 8 days). The length of the continuation period (when applicable) varied from country to country, up to until FBT was commercially available in that country.

General Design and Methodology: The study included a screening period, a randomized open-label dose titration period, an open-label treatment period, and an optional open-label continuation period.

At screening (visit 1), eligibility for study entry was determined, informed consent obtained and background information was collected. Patients received a screening-period diary to provide information on their BTP episodes throughout the screening period. At visit 2, patients who continued to meet the inclusion/exclusion criteria were randomly assigned to 1 of the 2 titration groups with a starting dose of FBT of either 100 mcg (group A) or 200 mcg (group B). During the open-label titration period, FBT was individually titrated for each patient to an effective FBT dose. Patients were provided with a titration-period diary to monitor the titration process. Once the effective dose of FBT had been identified, the patient returned to the study center for the next visit (visit 3).

Patients who reached an effective dose entered the open-label treatment period, where the patient treated up to 8 episodes of BTP with the study drug during a maximum 8-day period. Each patient was supplied with 8 treatments (8 tablets of FBT) at the effective dose determined during the titration period. The patients recorded time to meaningful pain relief and assessed the medication performance for each episode of BTP for which FBT was used. Patients returned to the study center for the next visit (visit 4).

Patients continued taking their opioid maintenance medication throughout the study. If the patient experienced consistently more than 4 BTP episodes per day, the dose of the opioid maintenance used for persistent pain was re-evaluated and the patient was withdrawn from the study.

Patients who completed the open-label treatment period in countries where FBT was not available after visit 4 (France, Italy, Poland, and Spain) had the option to enter an open-label continuation period. The continuation period ended as soon as FBT was commercially available in their country. Each patient was supplied with FBT at the effective dose for a 4 week period. The patients returned to the study center every 4 weeks for safety assessments.

Primary Efficacy Measure and Endpoint: The primary efficacy variable was the percentage of patients reaching an effective dose by titration. The percentage of patients for whom the effective dose of FBT was reached with a starting dose of 100 mcg (group A) was compared to the percentage of patients for whom the effective dose of FBT was reached with a starting dose of 200 mcg (group B). The effective dose was the dose that, for 2 consecutive BTP episodes, provided adequate analgesia within the first 30 minutes after administration of study drug and that minimized undesirable effects. The assessment was performed by the patient and was reported in the titration-period diary. Thirty (30) minutes after the start of administration of the dose, the patient estimated if adequate analgesia was reached at the dose used and answered the following questions:

Q1. Did this dosage provide you with a satisfactory relief since it was taken? Yes/No

Q2. Did you feel this dosage was acceptable without undesirable effect? Yes/No

If these 2 questions were answered with 'Yes,' this dose was the effective dose. The next BTP episode was used to confirm the effective dose, and if confirmed, the effective dose was used for all following BTP episodes. If Q1 answer was 'No', a second dose at the same strength was used for the same BTP episode, provided the answer to Q2 was 'Yes'. If the patient had already taken the study treatment twice for the same BTP episode (ie, after the second period of 30 minutes), the patient took the usual rescue medication and the next higher dose was used for the next BTP episode. If Q2 answer was 'No', this dose was not appropriate for the patient, the usual rescue medication was taken, and the patient was withdrawn from the study. The only exception to this was if the unacceptable dose was the starting dose of 200 mcg in titration group B, where the patient decreased the dose and treated the next BTP episode with a 100 mcg dose. If the patient had achieved an effective dose but experienced consistently more than 4 BTP episodes per day, the dose of the opioid maintenance used for persistent pain was re-evaluated and the patient was withdrawn from the study.

Secondary Efficacy Measures and Endpoints: The secondary efficacy measures and endpoints are as follows:

- **Time to Meaningful Pain Relief:** During the treatment period, the patient assessed for each BTP episode the time to reach a meaningful pain relief after FBT intake (recorded by stopwatch). If after 60 minutes meaningful pain relief was not achieved or the patient decided to take rescue medication, the patient stopped the watch and recorded 'no meaningful pain relief' in the diary (ie, patient was censored).
- **Use of Standard Rescue Medication:** Any use of standard rescue medication after the administration of study drug for relief of BTP was recorded in the patient's diary. In the titration period, patients were permitted to take their usual rescue medication for episodes of BTP if adequate pain relief for 1 episode was not achieved 60 minutes after the combined dose of FBT (with the exception of an initial dose of 800 mcg where the patient was permitted to take their usual rescue medication after the initial 30 minutes, not take a second dose of FBT, and were withdrawn). In the treatment period, patients were permitted to take their usual rescue medication for episodes of BTP if adequate pain relief was not achieved 30 minutes after the initial administration of FBT.

- **Medication Performance Assessment:** A medication performance assessment was recorded 30 and 60 minutes after the administration of study drug during the treatment period. The patient answered the following question: "How well did your study medication perform in controlling this breakthrough pain episode?". The answer was measured on a 5-point Likert type scale.
- **Global Assessment by the Patient:** The patient's global assessments were performed at visit 2 (Patient Satisfaction only) and visit 4 (or early termination) assessing: Patient Satisfaction (5-point scale); Ease of Use (4-point scale); and Patient's Global Impression of Change (PGIC) (7-point scale).
- **Quality of Life of the Patient:** The patient rated his/her quality of life and functional status using the 7-item Interference Subscale of the Brief Pain Inventory-short form questionnaire (BPI-7S), assessed on an 11-point scale.

Safety Variables: Safety was assessed by evaluating: reported adverse events (including deaths, serious adverse events and withdrawals due to adverse events), background pain intensity, vital signs measurements, physical examination findings, oral mucosal examinations, and concomitant medication usage. The adverse events for patients with fentanyl based maintenance therapy were compared to those with other opioid maintenance therapy. In addition, in order to comply with the risk minimization action plan commitments, reports for misuse, abuse, and diversion were recorded.

Statistical Considerations: Given the titration success rate of 65% seen in previous studies, a total of 880 patients (440 per group) needed to be included in the titration period to have 80% power to demonstrate the non-inferiority of starting with a 200 mcg dose to that with a 100 mcg dose. This estimate was based on the large-sample normal approximation test of proportions with a one-sided 0.050 significance level. Further assuming a 75% screening success rate, approximately 1180 patients needed to be screened. The primary efficacy variable was analyzed by estimating the effective dose rate (ie, number of patients reaching an effective dose divided by the total number of patients in the titration group) in each randomized titration group and comparing the confidence interval (CI) for the difference, calculated as 100 mcg - 200 mcg, using the TSAF analysis set. Non-inferiority was established if the upper bound of the two-sided 90% CI was less than 8%. Kaplan-Meier analysis was used to estimate the distribution of time to meaningful pain relief over all. All baseline data and primary efficacy data were summarized by randomized titration group and overall, unless otherwise noted. Secondary efficacy data were summarized overall. Safety data during the titration period were summarized by randomized titration group and overall. Safety data during the treatment and continuation periods were summarized overall.

Summary of Results

Patient Disposition and Demography: The number of patients screened and randomized was lower than planned due to recruitment difficulties. A total of 442 patients were screened for enrollment into this study. Three hundred and thirty (330) patients (74.7% of those screened) were considered to be eligible for enrollment into the study and were randomized.

The titration groups were well matched with respect to demographic characteristics (age, sex, and weight). Baseline characteristics for cancer history (primary tumor or hematologic malignancy site), persistent cancer pain, BTP assessment, physical examination, and oral mucosal examination were generally similar between patients in both titration groups.

Efficacy Results:

Primary Efficacy Variable: The effective dose rate was numerically higher in the 200 mcg titration group compared to the 100 mcg titration group (81.4% vs 75.2%). Despite the loss of power due to the reduced sample size, non-inferiority is established in this study as the upper limit of the two-sided 90% CI for the difference in effective dose rate (1.4%) was lower than 8%, and it can be concluded that a starting dose of 200 mcg FBT is not worse than a starting dose of 100 mcg FBT by more than 8%. Overall, the 2 most frequently reported effective doses of study drug as assessed by the investigator at the end of the titration period were 200 mcg (39.6% of patients), and 400 mcg (26.9% of patients). There was a slight difference in the investigator-confirmed effective dose between patients in the 100 mcg titration group and the 200 mcg titration group. The most frequently reported effective dose of study drug for both titration groups was 200 mcg (33.9% and 44.1% for the 100 mcg titration group and 200 mcg titration group, respectively), whereas the 100 mcg dose was reported as the effective dose of study drug for 31.2% of patients in the 100 mcg titration group and 5.1% of patients in the 200 mcg titration group, and the 400 mcg dose was

reported as the effective dose of study drug for 22.0% of patients in the 100 mcg titration group and 30.9% of patients in the 200 mcg titration group.

Secondary Efficacy Variables:

Time to Meaningful Pain Relief: A total of 1810 episodes of BTP were recorded during the treatment period and meaningful pain relief was achieved for 1576 (87.1%) episodes. The median time to meaningful pain relief (Kaplan-Meier analysis) was 19 minutes over all BTP episodes.

Use of Standard Rescue Medication: There were 2610 episodes of BTP in the titration period (when looking for the effective dose of FBT), 3.9% of which required rescue medication. There were 1810 episodes of BTP in the treatment period, 8.5% of which required rescue medication.

Medication Performance Assessment: Over all episodes of BTP in the treatment period, responses for the 1776 episodes of BTP at 30 minutes after medication were 'good' (40.1%), 'very good' (24.4%), and 'excellent' (5.8%) for a total of 70.3% (1248/1776) of episodes, and responses for the 1668 episodes of BTP at 60 minutes after medication were 'good' (38.7%), 'very good' (35.0%), and 'excellent' (8.6%) for a total of 82.3% (1374/1668) of episodes.

Quality of Life of the Patient: The BPI-7S questionnaire indicated that the quality of life and functional status of the patients had improved between visit 2 and visit 4 for each of the subscales. The Global Score showed a mean change (improvement) of -8.6 and the 95% CI was (-10.5, -6.7), which showed a favorable effect of the study drug on the patient's quality of life.

Global Assessment by the Patient: The patient's global assessment evaluated Patient Satisfaction, Ease of Use, and PGIC. For Patient Satisfaction, the patients' responses to all questions were rated higher at the end of the treatment period (visit 4) compared to baseline (visit 2). Evaluation of 'Ease of Use' showed that the majority of patients found the treatment easy/convenient to use; 51.2% of patients found the treatment 'easy' to use, and 32.1% of patients found the treatment 'very easy' to use. The PGIC from the start of study was an improvement to overall status for the majority of patients (155/208; 74.5%). This indicated a generally positive outcome for the PGIC following treatment of BTP with the study drug.

Safety Results:

Adverse Events: The most frequently observed adverse events in all study periods were characteristic for patients with long-term cancer, disease progression, and/or those treated with oral transmucosal fentanyl containing products (and any other opioid therapy) (ie, nausea, malignant neoplasm progression, somnolence, vomiting, dizziness, anaemia, and application site reactions). The types of adverse events (ie, system organ class and preferred term) were similar between the titration period, the treatment period, and the continuation period. In the titration and treatment periods, the majority of adverse events were reported as mild or moderate in severity, and in the continuation period, the majority of adverse events were reported as severe or moderate. The majority of severe adverse events in the continuation period were due to cancer disease progression.

When safety results were compared between patients receiving fentanyl based maintenance therapy and patients receiving other opioid maintenance therapy, the percentages of patients with adverse events (66.9% and 62.3%, respectively), serious adverse events (24.8% and 18.6%, respectively), adverse events considered related to study drug (24.1% and 24.0%, respectively), adverse events leading to withdrawal (21.4% and 16.2%, respectively), and adverse events with a fatal outcome (17.9% and 13.8%, respectively) were not substantially different between patients receiving fentanyl based maintenance therapy and patients receiving other opioid maintenance therapy.

The majority of serious adverse events (including those with a fatal outcome) were considered to be related to the underlying disease. The most frequently observed serious adverse events were lung neoplasm malignant, malignant neoplasm progression, renal failure, and respiratory failure. The most frequently observed adverse events leading to discontinuation of the study drug in the titration period were nausea and vomiting, and in the long term (ie, in the continuation period) the most frequently observed adverse event leading to discontinuation was malignant neoplasm progression.

Vital Signs: There were no clinically meaningful trends in mean changes from baseline for any vital signs variables and no clinically meaningful differences between the 100 mcg and 200 mcg titration groups. There were no clinically meaningful trends during the continuation period.

Concomitant Medications: Medications most frequently used by patients during the study included analgesics (99.1%), drugs for acid related disorders (50.7%), anti-inflammatory and antirheumatic products (34.5%), laxatives (33.6%), corticosteroids for systemic use (33.2%), psycholeptics (31.8%), drugs for functional gastrointestinal disorders (30.9%), and psychoanaleptics (30.5%).

Background Pain Intensity: Background pain intensity scores were stable throughout the study from the screening period to the titration and treatment periods. The median total scores for all periods were 4.0 (mild pain), on an 11-point numerical rating scale from 0='no pain' to 10='pain as bad as you can imagine', indicating that background pain was well-controlled.

Abnormal Oral Mucosal Examination Findings: At visit 3 (ie, after the titration period, N=223), 4 patients had a clinically significant change from the previous visit (from normal to abnormal) that was considered related to study drug tablet placement. At the final visit (visit 4) or early termination (ie, after the treatment period, N=211), 3 patients had a clinically significant change from the previous visit (from normal to abnormal) that was considered related to study drug tablet placement.

Physical Examination Findings: There were few newly diagnosed physical examination findings (defined as being 'normal' or 'missing' at baseline and abnormal at the post-baseline assessment). The head, eyes, ears, nose and throat (HEENT) and chest and lungs were the body systems with the most commonly reported newly diagnosed abnormal physical examination findings at the final visit (both 6 patients).

Study Drug Misuse, Abuse, and Diversion: In the titration and treatment periods combined, 3 (1.0%) patients in the TSAF analysis set were withdrawn from the study due to study drug misuse or diversion. In the continuation period, 2 (2.3%) patients in the CSAF analysis set were withdrawn from the study due to study drug abuse. It was considered by Cephalon that no adverse event was linked to any misuse/abuse/diversion reported, and moreover, misuse/abuse/diversion cases as reported by the investigators did not meet the definitions in the protocol but were considered to be related to non-compliance with the study drug.

Long-term Safety: There were no long-term safety concerns based on evaluation of adverse events, vital signs, physical examination, and oral mucosal examination data.

Conclusions: Despite the loss of power, it is considered that non-inferiority of the 200 mcg starting dose of FBT compared to the 100 mcg starting dose is established in this study. Evaluation of the time to meaningful pain relief, use of standard rescue medication, medication performance assessment, quality of life, and patient's global assessment all support the analgesic efficacy of FBT. The safety data do not indicate any new safety concerns with either short-term or long-term use of FBT at doses up to 800 mcg per BTP episode.