Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Fentanyl citrate

Proprietary Product Name: Fentora

Sponsor: Orphan Australia Pty Ltd

31 March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of the most common abbreviations

Abbreviation	Meaning
λz	Apparent plasma terminal elimination rate constant
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Around-the-clock
$AUC_{0-\infty}$	Area under the plasma drug concentration-versus-time curve from time 0 to infinity after study drug administration
AUC_{0-24}	Area under the plasma drug concentration-versus-time curve from time 0 to 24 hours after study drug administration
AUC_{0-72}	Area under the plasma drug concentration-versus-time curve from time 0 to 72 hours after study drug administration
BMI	Body mass index
BPI-7S	7-item Interference Subscale of the Brief Pain Inventory–Short Form
BPI-SF	Brief Pain Inventory-Short Form
Bpm	Beats per minute
BTP	Breakthrough pain
BUN	Blood urea nitrogen
CAPF	Clinician Assessment of Patient Function
CGIC	Clinical Global Impression of Change
CL	Total plasma clearance
CL/F	Apparent total plasma clearance normalised for systemic bioavailability
C_{max}	maximum observed serum drug concentration

Abbreviation	Meaning
CNS	Central nervous system
COAD	Chronic obstructive airways disease
CSR	Clinical Study Report
CYP	Cytochrome P450
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration (USA)
FEBT	Fentanyl effervescent buccal tablet
F_{OVF}	Absolute bioavailability of transmucosal Oravescent FEBT
GAS	Goal Attainment Scale
GMPA	Global medication performance assessment
IV	Intravenous
Kel	Terminal elimination rate constant
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MPA	Medication performance assessment
M-PEM	Modified Prescription-Event Monitoring
MPI	Multidimensional Pain Inventory
NA	Not applicable
NAV	Not available
NOS	Not otherwise specified
OTFC	Oral transmucosal fentanyl citrate

Abbreviation	Meaning
OVF	Oravescent fentanyl (citrate) = FEBT
PADER	Periodic Adverse Drug Experience Reports
PAF	Patient Assessment of Function
PASS	Pain Anxiety Symptoms Scale
PFTS	Pain Flare Treatment Satisfaction
PGIC	Patient Global Impression of Change
PI	Product Information
PI	Pain intensity
PID	Pain intensity difference
POMS	Profile of Mood States
PSUR	Periodic Safety Update Report
RBC	Red blood cell
RMP	Risk Management Plan
SD	Standard deviation
SE	Standard error
SF-36	Short Form Health Survey-36
SI	International System of Units
SPID	Sum of pain intensity differences
$SPID_{30}$	SPID up to 30 minutes after the start of study drug administration
$SPID_{60}$	SPID up to 60 minutes after the start of study drug administration
SpO_2	oxyhaemoglobin saturation
SQ	Sleep questionnaire
T½	Elimination half-life
T_{max}	Time to maximum observed plasma drug concentration

Abbreviation	Meaning
TOTPAR	Total pain relief
U	Unknown (missing)
UK	United Kingdom
ULN	Upper limit of normal
USP	United States Pharmacopeia
V	Volume of distribution
V/F	Apparent volume of distribution normalised for systemic bioavailability
WBC	White blood cell
WHO	World Health Organization
WHO	Drug World Health Organization (WHO) drug dictionary
WPAI	Work Productivity and Activity Impairment Questionnaires
y, yr	Year(s)

1. Clinical rationale

The ability to achieve a rapid analgesic effect is important in the management of pain for patients with cancer who, despite continuous background analgesia, often experience recurrent episodes of acute transitory pain otherwise known as breakthrough pain (BTP). Opioid analgesics are standard treatment for patients with cancer pain and there are a number of marketed opioid drugs in a range of formulations, used for the management of both background pain and BTP. However, the effectiveness of currently available products used in the management of BTP is limited by their mode of administration, lag time to adequate analgesia and long duration of action.

The prevalence of BTP is high, with 64% to 89% of patients with chronic cancer pain experiencing such events. BTP is usually severe and achieves peak intensity in 3 to 5 minutes, and the median duration is 30 minutes. Patients with BTP are usually treated with short acting or normal release opioid analgesics. In contrast, background pain is continuous throughout the day (≥12 hours/day) and is managed with around the clock (ATC) medication, usually in the form of long acting or sustained release opioid formulations.

For patients taking opioids as their ATC medication, it is recommended that they also take opioids for BTP. The method of determining the most effective dose of an opioid remains an inexact science, with little correlation between the dose of daily ATC opioid and the opioid dose needed for BTP. Episodes of BTP vary in cause, severity, and duration and thus, medication to manage BTP should be titrated individually, in a fashion similar to that used for opioid medications given for continuous background pain.

Fentanyl is suited for the management of BTP for the following reasons: greater potency than morphine, shorter duration of action, lack of ceiling effect on analgesia, analgesic effects related to blood levels and rapid buccal absorption avoiding extensive first pass metabolism. FEBT was developed using proprietary technology for efficient delivery with the aim of enhanced rate and extent of absorption.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The objective of the initial drug development program was to develop a buccal dosage form of fentanyl citrate using effervescence in the tablet to facilitate absorption transmucosally in order to achieve therapeutically effective blood levels with lower doses of fentanyl than those in Actiq®, an oral transmucosal fentanyl citrate drug product, which is approved in a number of countries worldwide. The fentanyl buccal tablet was designed to disintegrate in the buccal cavity at approximately the same rate as Actiq®. However, due to the differences in PK profiles observed between the fentanyl effervescent buccal tablet (FEBT) and Actiq® it was decided that clinical efficacy and safety studies should be conducted and the objective was no longer to show bioequivalence. As a result a number of studies with the earlier formulations were included in the submission for completeness, but have not been evaluated as part of this report.

The submission contained the following clinical information:

- 16 clinical pharmacology studies, including 15 that provided pharmacokinetic data and 1 that provided pharmacodynamic data
- 2 pivotal efficacy/safety studies
- 2 other efficacy/safety studies

- 7 studies of efficacy/safety in other indications which are not the indication being sought in this submission. These studies have been reviewed for safety but not evaluated for efficacy
- 14 (other, eg. 13 x PSURs, 1 drug utilisation study).

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The study reports state that all studies were conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH) and any applicable national and local laws and regulations (eg, in USA - Title 21, Code of Federal Regulations [21 CFR] Parts 50, 54, 56, 312, and 314). Before the studies were initiated, the protocol was submitted to the Institutional Review Board (IRB) according to national or local regulations and written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1: Submitted pharmacokinetic studies studies.

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose	1029	PK
	- Multi-dose	1029	PK
		099-20	PK
	Dose proportionality (single dose)	099-18	PK
		1027	PK
		1037	PK
		1052	PK
		099-19	PK Japanese
		1054	PK Japanese
	Bioavailability		
	- absolute and relative	1028	BA
	- comparison of strengths	099-21	BA

PK topic	Subtopic	Study ID	Primary aim
	Bioequivalence		
	Different strengths	1026	BE
	Buccal vs sublingual	1043	BE
	Oravescent vs Actiq	099-11	BE
	Different strengths	1053	BE
PK in special populations	Target population § - Single dose - Multi-dose	099-16	PK

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

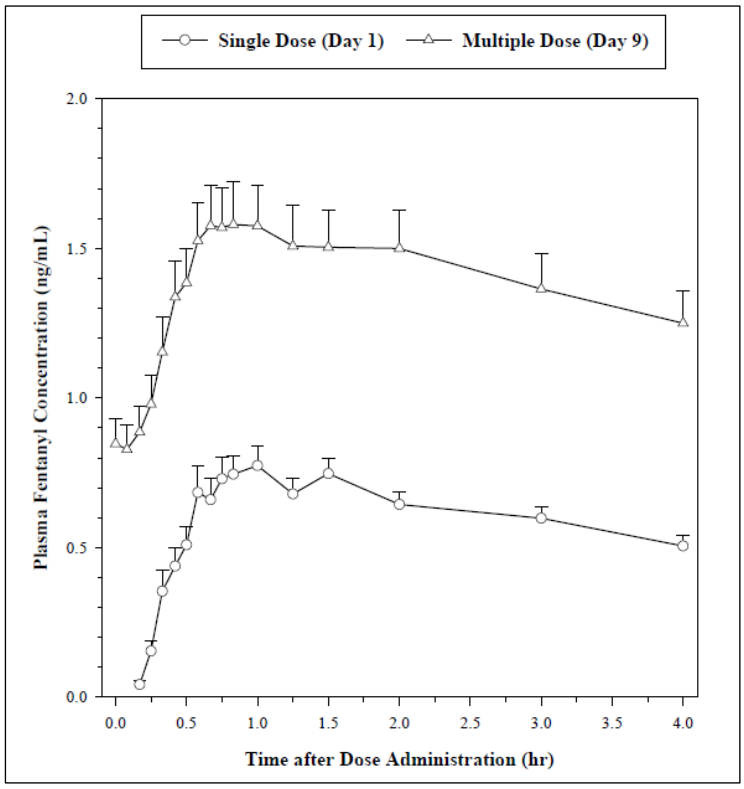
3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Absorption

The absorption profile of FEBT is largely the result of an initial rapid absorption through the buccal mucosa, with peak plasma concentration attained 50 minutes after single and multiple dose administration in the fasted state. Approximately 50% of the total dose administered is absorbed transmucosally and rapidly becomes systematically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

Study 1029 was an open label, single and multiple dose study conducted in 24 healthy men and women to assess the PK of single and multiple doses. The following figure shows the mean plasma concentrations following a single 400 µg dose and 21 multiple doses of FEBT.

Figure 1: Mean (SEM) plasma concentration versus time profiles following single and multiple doses of 400 µg doses of FEBT in healthy subjects



3.2.2. Bioavailability

3.2.2.1. Absolute bioavailability

The absolute bioavailability was determined in **Study 1028** in which 29 patients received both a single oral 400 µg transmucosal dose of FEBT and an intravenous infusion of 400 µg of fentanyl administered over approximately 5 minutes. The absolute bioavailability was 65%.

3.2.2.2. Bioequivalence of clinical trial and market formulations

No bioequivalence study was done comparing the Generation III formulation and the formulation intended for marketing. The Generation III formulation was used for all the clinical pharmacology and efficacy and safety studies in the submission. The only difference between Generation III and the commercial formulation was the removal of the colorants from the tablets.

3.2.2.3. Bioequivalence of different dosage forms and strengths

Study 1043 was conducted in 90 subjects to assess the PK of one 400 µg FEBT administered buccally versus sublingually to assess whether systemic exposure is affected by the site of tablet placement. Similar PK profiles, meeting the criteria for bioequivalence, were observed following buccal and sublingual administration.

Study 1026 was an open label, 2 treatment, 3 period crossover study in 27 subjects designed to assess the bioequivalence between multiple lower dose tablets (4 X 100 µg) tablets and one higher dose tablet (1 x 400 µg tablet). The results did not show bioequivalence, patients would experience a slight decrease in exposure upon conversion to a single higher strength tablet (approximately 12% and 13% lower C_{max} and $AUC_{(0-\infty)}$). The potential impact of this decrease on pain relief has not been evaluated clinically but would be covered in the proposed individual titration period.

Study 099-21 was an open label randomised, 3 treatment, 3 period crossover study conducted in 29 healthy Japanese subjects to compare the PK of two 200 µg tablets to one 400 µg tablet and two 200 µg tablets administered 30 minutes apart. The results indicated that treatment with one 400 µg FEBT and simultaneous administration of two 200 µg tablets were bioequivalent. For treatment with one 400 µg tablet, a smaller and significantly different T_{max} value was observed compared with the T_{max} values for treatment with two 200 µg tablets administered simultaneously and 30 minutes apart. Longer T_{max} and smaller C_{max} values were observed after treatment with two 200 µg tablets 30 minutes apart compared with one 400 µg tablet.

3.2.2.4. Bioequivalence to relevant registered products

The relative PK profiles of FEBT compared to the currently registered transmucosal lozenge Actiq® was also investigated in Study 1028. The fraction of the FEBT dose absorbed transmucosally is approximately 50% of the total dose (f_{TM}=0.48), and the fraction of the Actiq dose absorbed transmucosally is approximately 25% of the total dose (f_{TM}=0.22). As a result, FEBT demonstrates a higher absolute bioavailability (F_{OVF}=0.65) when compared to Actiq (F_{ACTIQ}=0.47).

Following dose normalisation to equal doses (ie 400 µg fentanyl) FEBT demonstrated an approximately 30% higher exposure than fentanyl from Actiq (as measured by C_{max}, $AUC_{(0-\infty)}$ and $AUC_{(0-Tmax)}$). Following normalisation for comparable C_{max} values (400 µg of FEBT and 800 µg of Actiq [normalised to 600 µg]), fentanyl from FEBT has shown the potential to achieve higher earlier systemic exposure compared with Actiq (as measured by $AUC_{(0-Tmax)}$). Based on these results an approximately 30% smaller dose of FEBT should be selected to achieve systemic exposures comparable with those following administration with Actiq.

3.2.2.5. Influence of food

No formal clinical PK studies were conducted to assess the effect of food on the PK of fentanyl formulated as FEBT. Due to the extent of transmucosal absorption of fentanyl administration of the effervescent formulation, administration with food is not expected to affect early systemic exposure.

3.2.2.6. Dose proportionality

Dose proportionality was evaluated in three studies that included dose ranges as follows: 100 µg through 800 µg in Study 1027, 600 µg through 1200 µg in Study 1037 and 600 µg through 1300 µg in Study 1052.

In Study 1027, it was shown that total systemic exposure increases in a dose proportional manner over the 100 through 800 µg planned therapeutic dose range of FEBT, as reflected by the approximately dose proportional increases in mean C_{max} and mean $AUC_{(0-\infty)}$ following single dose administration.

In Study 1037, it was shown that total systemic exposure, as measured by $AUC_{(0-\infty)}$, increases in a dose proportional manner over the 600 through 1200 µg dose range of FEBT, as reflected in the dose proportional increases in mean $AUC_{(0-\infty)}$ following single dose administration. Systemic exposure, as measured by C_{max} was shown to be dose proportional with the exception of the 1200 µg dose, which was slightly less than dose proportional.

In Study 1052, it was shown that total systemic exposure increases in a dose proportional manner over the 600 though 1300 µg planned therapeutic dose range of FEBT, as reflected in the approximately dose proportional increases in mean C_{max}, mean $AUC_{0(0-t)}$ and mean $AUC_{(0-\infty)}$ following single dose administration.

3.2.3. Distribution

3.2.3.1. Volume of distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system with a large apparent volume of distribution of approximately 1100 L following IV dose of fentanyl and an apparent volume of distribution of 1500 L following a single dose of FEBT (**Study 1028**). After administration of FEBT, fentanyl undergoes initial rapid distribution that represents an equilibration of fentanyl between plasma and the highly perfused tissues (brain, heart and lungs). Fentanyl reaches the deep tissue compartment at a slower rate compared with the highly perfused tissues.

3.2.3.2. Plasma protein binding

No formal studies were specifically conducted to assess the plasma protein binding of fentanyl in support of the FEBT formulation. The plasma protein binding of fentanyl is 80% to 85%. The main protein is alph-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

3.2.4. Metabolism

No formal studies were specifically conducted to assess the metabolism of FEBT. There is no reason to believe that administration by the transmucosal route would alter the metabolic pathways. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is primarily metabolised in the liver and in the intestinal mucosa to norfentanyl by cytochrome CYP3A4 isoforms. Other metabolites represent only a minor portion of the fentanyl dose. Preclinical studies have found that norfentanyl and minor metabolites were not found to have significant pharmacological activity.

3.2.5. Excretion

Disposition of fentanyl after administration as FEBT has not specifically been characterised in a mass-balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkyalated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important.

Following absorption, fentanyl formulated as FEBT exhibits an apparent biexponential or triexponential decline from peak plasma concentration. The terminal elimination phase of fentanyl formulated as FEBT is difficult to describe, consistent with redistribution between plasma and a deep tissue compartment. This was investigated in a number of studies (Studies 1026, 1027, 1028, 1029, 1037, 1043 and 1046). Elimination is slow with a median terminal half-life (T½) of approximately 22 hours, which is consistent with the T½ observed following intravenous fentanyl (approximately 18 hours). The mean total plasma clearance of IV fentanyl is approximately 42 L/hr.

Despite its long T½ fentanyl is known to exhibit a short duration of action that is consistent with rapid and extensive uptake of fentanyl in highly perfused tissues. This rapid uptake, as well as the redistribution of fentanyl between a deep tissue compartment and the plasma, results in plasma concentrations that decrease rapidly to below a clinically relevant threshold.

3.2.6. Pharmacokinetics in other special populations

3.2.6.1. Pharmacokinetics in subjects with impaired hepatic or renal function

No formal studies of the effect of renal or hepatic impairment on the PK of fentanyl formulated as FEBT were conducted. Although fentanyl kinetics are known to be altered as a result of hepatic and renal disease due to alterations in metabolic clearance and plasma protein binding, the duration of effect for the initial dose of fentanyl is largely determined by the rate of

distribution of the drug. Diminished metabolic clearance may therefore become significant, primarily with repeated dosing or at very high single doses. It is recommended that FEBT is titrated to clinical effect in all patients and special care should be taken in patients with severe hepatic or renal disease.

3.2.6.2. Pharmacokinetics according to age

No formal clinical PK studies were conducted to study the effect of age. The mean age of all subjects in the pooled database was 28.4 years and most subjects were aged 45 years or younger.

3.2.6.3. Pharmacokinetics in patients with cancer with or without mucositis

Study 099-16 was conducted in 16 opioid tolerant adult patients with cancer with or without oral mucositis. All patients received a single 200 µg dose of FEBT. A statistical comparison of the plasma fentanyl PK parameters between patients with and without mucositis showed no significant differences between the groups on the basis of the ratio of geometric means for AUC(0-tmax'), AUC(0-8), and Cmax, and no difference between groups in median Tmax. Following a single 200 µg dose, systemic exposure, as measured by AUC(0-8) was 25% higher in opioid tolerant patients with cancer with mucositis than in those without mucositis. However, the numbers in the study are small and firm conclusions should be made with caution.

3.2.7. Pharmacokinetic interactions

No drug interactions studies have been conducted with FEBT.

Fentanyl is known to be primarily metabolised in the liver and intestinal mucosa by the cytochrome CYP3A4 isoforms to norfentanyl. Drugs that inhibit CYP3A4 activity may increase the bioavailability of swallowed fentanyl by decreasing intestinal and hepatic first pass metabolism and may decrease the systemic clearance of fentanyl. The concomitant use of potent CYP3A4, such as ritonavir, with FEBT may result in an increase in fentanyl plasma concentrations which could increase or prolong both the therapeutic effect and adverse events, and may cause respiratory depression. Drugs that induce CYP3A4/5 activity may decrease the bioavailability and increase the systemic clearance of fentanyl.

3.2.8. Effect of dwell time

Dwell time was defined as the time between tablet placement and the complete disappearance of tablet residue from the oral cavity, determined by visual inspection. An exploratory analysis of T_{max} and dose normalised $AUC_{(0\text{-}Tmax')}$ and C_{max} values versus dwell time was performed for individual subject data obtained in Studies 099-11 and 099-18. Despite a relatively large intersubject variability in dwell time, visual inspection of the plots demonstrated with the rate and extent of the buccal absorption of fentanyl formulated as FEBT was not affected by the dwell time. The average dwell time was 14 to 25 minutes.

3.3. Evaluator's overall conclusions on pharmacokinetics

The PK studies for FEBT were consistent with the known information for fentanyl. The submission contained the necessary studies to document those aspects of the PK of FEBT that were expected to be unique given its novel formulation.

Fentanyl formulated as FEBT is readily absorbed, with an absolute bioavailability of 65% following buccal administration. The absorption profile is largely the result of initial rapid absorption from the buccal mucosa, with peak plasma concentration attained at approximately 50 minutes in the fasted state. The mean PK profile based on the pooled data demonstrates that within 25 minutes, plasma concentrations reach approximately 80% of the C_{max} and are maintained through 2 to 3 hours after the start of administration. Approximately 50% of the total dose administered is absorbed across the buccal mucosa and rapidly becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged

absorption from the gastrointestinal tract. Following absorption, fentanyl formulated as FEBT exhibits an apparent bioexponential or triexponential decline from peak plasma concentration. The metabolism and excretion are as expected for fentanyl.

Multiple studies were conducted to demonstrate that fentanyl formulated as FEBT exhibits linear pharmacokinetics. Dose proportionality was not found in all the studies, which is explained in some of the study reports as being due to low numbers and in others to be due to decreased absorption due to taking multiple tablets to achieve the highest doses. There appears to be dose proportionality at doses from 100 to 800 µg and likely up to 1000 µg. Above this dose the largest study demonstrated dose proportionality up to 1300 µg. The lack of dose proportionality, if it exists, is unlikely to create problems as the results approximate dose proportionality and all patients should be individually titrated to the effective dose.

The rate and extent of fentanyl absorption of FEBT are not affected by the dwell time and there is no difference in the PK profile between buccal and sublingual placement of the tablet.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

Table 2: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	Primary aim
Primary Pharmacology	Effect on analgesic potency	1046	PD

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

Fentanyl citrate is a potent opioid analgesic with an analgesic potency approximately 80 times that of morphine. Fentanyl, a pure opioid agonist, acts primarily through interaction with µ-opioid receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

Study 1046 was a randomised, double blind, placebo controlled, 5 period cross over, single dose study conducted in 33 healthy men and women. The primary objective of the study was to examine the relative analgesic potency of the fentanyl buccal tablet (100 µg and 400 µg) as compared with that of IV morphine (2 and 8 mg) on thermally induced hyperalgesia as measured by the sum of pain intensity differences (SPID) derived from 100 mm VAS pain intensity scores over the first 60 minutes after study drug administration in healthy subjects. A secondary objective was to examine the PK/PD relationship of 100 µg FEBT, 400 µg FEBT, 2 mg

and 8 mg of IV morphine in healthy subject with thermally induced hyperalgesia. Naltrexone was not administered in this study.

Using the $SPID_{60}$ failed to demonstrate a significant difference from placebo for either of the high doses (400 µg FEBT or 8 mg IV morphine) at 42°C and 46°C, but there was a significant difference from placebo for the response to treatment using the $SPID_{60}$ at 49°C. Comparison of the $SPID_{60}$ following the 49°C thermal application between the high and low doses of each study drug and between FEBT and morphine demonstrated proportionality with p-values of 0.5285 and 0.0056 for parallelism and nonzero slope, respectively. Relative potency of FEBT to morphine assessed by $SPID_{60}$ at 49°C was 46.2. It was noted that there was substantial variability in the $SPID_{60}$ data, as evidenced by the broad range of 95% CIs in the relative potency estimates.

4.3. Evaluator's overall conclusions on pharmacodynamics

Only one PD study (Study 1046) of FEBT was submitted. Analgesic efficacy was tested in healthy volunteers with thermally induced hyperalgesia. The primary PD variable was the $SPID_{60}$ (sum of pain intensity scores averaged for each temperature at each time point over the 1st hour). The criteria for significance were not met for this variable. The study utilised an experimental pain model in healthy subjects rather than in patients with chronic pain. There was no significant difference from placebo following the 43°C and 46°C thermal applications, which resulted in a lack of significant effect when averaging the responses from all 3 temperatures. PID and pupil diameter measurements 60 minutes following the 49°C thermal application showed comparable relative potency.

The implications of the results of this study are limited and it is noted that there is no discussion of the PD in the Summaries. Additionally, the results of this study are limited to the studied dose range and cannot be extrapolated to higher doses. The results of the efficacy studies found that the efficacy of FEBT was not influenced by age, sex, race, weight or BTP pathophysiology.

5. Dosage selection for the pivotal studies

In selecting FEBT dose strengths for the clinical efficacy studies, results from **Study 099-011** indicated that lower doses of FEBT (~50%) were required to achieve a similar effect to the of the oral transmucosal fentanyl lozenge (Actiq®). Results from **Study 1028** indicated that the dose of fentanyl from FEBT should be approximately 70% of that in an Actiq unit in order to obtain comparable plasma concentrations, rather than the 50% predicted from the earlier study. No standard dose was selected for the efficacy studies and all patients were individually titrated from a starting dose of 100µg to an individual effective dose. The effective dose was then used in the pivotal studies for the double blind comparison to placebo. No patient received more than 800 µg.

6. Clinical efficacy

6.1. Treatment of breakthrough pain

6.1.1. Pivotal efficacy studies

6.1.1.1. Study 099-14

A Multicentre, Double-Blind, Placebo-Controlled Study of ORAVESCENT® Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients.

6.1.1.1.1. Study design, objectives, locations and dates

A double blind, randomised, placebo controlled study conducted at 30 centres in the USA from April 2004 to January 2005.

Primary objective: To determine the clinical efficacy of Oravescent fentanyl when used to relieve breakthrough pain (BTP) in opioid tolerant patients with cancer who are receiving maintenance opioids.

Secondary objective: To determine the tolerability and safety of Oravescent fentanyl when used to relieve BTP in opioid tolerant patients with cancer who were receiving maintenance opioids.

All eligible patients were first tested with a 100 µg dose of Oravescent and observed for 2 hours to determine tolerability. If patients did not experience any intolerable adverse effects then they entered the open label dose titration period for up to 21 days to determine the successful dose (defined as the dose strength that provided sufficient pain relief within 30 minutes after dosing for 2 consecutive episodes of BTP that occurred at least 4 hours apart). At the next visit patients entered the double blind study in which the patients received 10 blinded study drug treatments for the treatment of 10 episodes of BTP. Following the 10 episodes patients returned to the study site for follow up.

6.1.1.1.2. Inclusion and exclusion criteria

Inclusion: male or female (non-childbearing potential) patients, at least 18 years old with a histologically documented diagnosis of a malignant solid tumour or a haematological malignancy causing cancer-related pain and an ECOG status of ≤2; and who had been receiving 60-100 mg of morphine/day or 50-300 µg of transdermal fentanyl or an oral morphine equivalent dose for at least a week for cancer related pain and was experiencing on average, but not necessarily every day, 1-4 episodes of BTP per day that were adequately controlled with a stable dose of standard rescue medication, typically a fast acting opioid.

Exclusion: opioid or fentanyl intolerance; using intrathecal opioids; had a procedure within 30 days that would alter pain or response to analgesia; was experiencing xerostomia or mucositis/stomatitis ≥grade 2; had sleep apnoea or active brain metastases with increased intracranial pressure; COAD with CO_2 retention or was at risk of significant bradycardia because of underlying heart disease; significant renal or hepatic impairment, history of substance abuse or psychiatric disease.

6.1.1.1.3. Study treatments

Patients in the dose titration period were dispensed an open label dose titration kit containing 2 tablets of each dosage strength of Oravescent fentanyl. Patients started titration with a single tablet of the lowest dosage strength of Oravescent fentanyl, 100 µg, placed buccally to treat an episode of BTP. The patient treated each episode with an escalating dose until they achieved a successful dose which was defined as the dose strength that provided adequate analgesia (sufficient pain relief within 30 minutes after placing a single tablet of that dose strength in the buccal cavity for each of 2 consecutive episodes of BTP that occurred at least 4 hours apart) without unacceptable adverse events.

In the randomised double-blind treatment period of the study (up to 21-days), patients received 10 blinded study drug treatments (7 Oravescent fentanyl tablets at the successful dose and 3 matching placebo tablets). During the double-blind treatment period of the study, patients served as their own controls by taking both Oravescent fentanyl and placebo tablets. Patients were instructed to take only 1 tablet of study drug for each BTP episode and not to administer additional study drug within 4 hours following any study drug administration. Patients were asked to refrain from using rescue medication for at least 30 minutes after study drug administration. All 10 doses were to be taken within a 21-day period.

The rescue medication was not specified but was described as the "patient's standard rescue medication". The rescue medication used included oxycodone/acetaminophen (24%), hydrocodone/acetaminophen (21%), morphine (17%), and hydromorphone 11%).

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was the sum of the pain intensity differences (SPID) through 30 minutes after the start of administration of study drug used for an episode of BTP during the double blind period ($SPID_{30}$).

$SPID_{30}$ was calculated as the sum of the pain intensity difference (PID) at both 15 and 30 minutes after administration of study drug for each BTP episode as follows: $SPID_{30} = PID_{15}+PID_{30}$.

Other efficacy outcomes included:

- SPID at each additional time point – $SPID_{15}$, $SPID_{45}$ and $SPID_{60}$
- Pain intensity difference (PID) value at each time point - PID_{15}, PID_{30}, PID_{45}, PID_{60}
- Pain relief (PR) score at each time point – PR_{15}, PR_{30}, PR_{45}, PR_{60}
- Total PR (TOTPAR) value at each time point - $TOTPAR_{15}$, $TOTPAR_{30}$, $TOTPAR_{45}$, $TOTPAR_{60}$
- Global medication performance assessment 30 and 60 minutes after administration of study drug
- Proportion of BTP episodes for which rescue medication was used, time from start of administration of study drug to use of rescue medication and relative risk of requiring rescue medication.

The PID and SPID were derived from patients' assessments of pain intensity (PI) recorded on visual scales in the patient diary. Patients rated the PI of each BTP episode by circling a number on a linear scale from 0 ("no pain") to 10 ("worst pain") (numbers 1 through 9 had no descriptive labels) before taking study drug and at 15, 30, 45, and 60 minutes after administration of study drug (the time at which a tablet was placed into the buccal cavity). A PID was calculated for each of the time points after administration of study drug by subtracting the PI at 15, 30, 45, and 60 minutes after administration of study drug from the PI at 0 minutes (PID_{15}, PID_{30}, PID_{45}, and PID_{60}, respectively).

Patients rated PR at 15, 30, 45, and 60 minutes after administration of study drug using a 5-point visual scale (0=none, 1=slight, 2=moderate, 3=lots, 4=complete).

TOTPAR was derived from PR scores. TOTPAR was calculated for each episode as the sum of PR scores at each quarter-hour assessment of PR until 60 minutes after administration of study drug, as follows: $TOTPAR_i=TOTPAR_{i-15}+PR_i$, where i=30, 45, and 60, and $TOTPAR_{15}=PR_{15}$.

A patient global medication performance assessment (0=poor, 1=fair, 2=good, 3=very good, 4=excellent) was also made at 30 and 60 minutes after administration of study drug.

6.1.1.1.5. Randomisation and blinding methods

This study included an initial open-label dose titration period followed by a double-blind, randomised, placebo-controlled treatment period. In the initial open label period the patients titrated the dose to achieve a successful dose. In the double-blind treatment period, Oravescent fentanyl tablets and matching placebo tablets were packaged at the successful dose so that neither the patient nor study centre personnel knew which treatment (Oravescent fentanyl or placebo) was in each treatment pack.

6.1.1.1.6. Analysis populations

Safety analysis set: included those patients in the set of enrolled patients who have received 1 or more doses of study drug during the open-label dose titration period of the study.

Intent-to-treat (ITT) or double-blind safety analysis set: included those patients in the safety analysis set who have received 1 or more doses of study drug during the double-blind treatment period of the study.

Full analysis set (or modified ITT set): included those patients in the double-blind safety analysis set who received study drug and treated at least 1 episode on Oravescent fentanyl and 1 episode on placebo during the double-blind treatment period, and had at least 1 pre-treatment PI score and 1 post treatment PI score for each of these episodes.

Evaluable analysis set: included those evaluable patients in the full analysis set who have at least 1 evaluable episode treated with Oravescent fentanyl and at least 1 evaluable episode treated with placebo during the double-blind treatment period.

6.1.1.1.7. Sample size

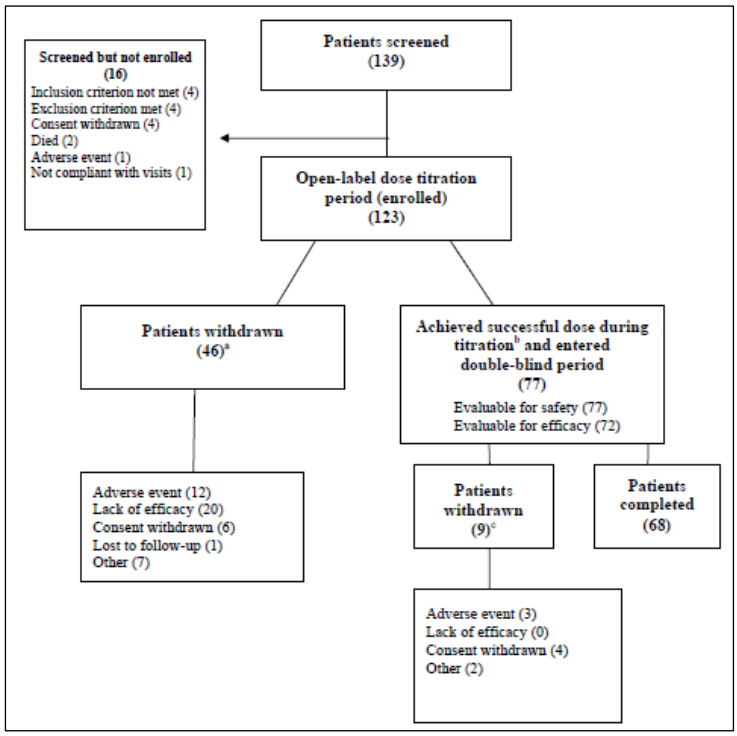
Sample-size estimates were based in part on a clinical study of similar design (ie, an open-label dose titration period and a double-blind, randomised, placebo-controlled period) reported for ACTIQ (Farrar et al 1998). On this basis, approximately 63 patients would be needed to evaluate efficacy during the double-blind period. This would provide over 95% power to detect a treatment difference of 1.4 between study drug and placebo in the primary efficacy variable, $SPID_{30}$, with a standard deviation of the within-patient difference not exceeding 3.00.

6.1.1.1.8. Statistical methods

The primary objective was tested using the primary efficacy variable, $SPID_{30}$, during the double-blind treatment period of the study comparing BTP episodes for which Oravescent fentanyl was used with BTP episodes for which placebo was used. The primary outcome was tested using an analysis of variance (ANOVA) with treatment and centre as fixed effects and patient as a random effect. The statistical test was two-tailed using $\alpha=0.05$. The consistency of treatment effects over different centres was evaluated by a separate ANOVA with treatment, centre, patient, and treatment-by-centre as factors. If there was evidence of a treatment-by-centre interaction (p-value ≤ 0.10), a descriptive summary of treatment differences for each centre was used to identify the nature of the interaction and the data were analysed as appropriate. In this case, the p-value reported was from a model with the interaction term included. The final model for the primary efficacy analysis was also the model for the secondary variables SPID and TOTPAR. No separate treatment by covariate interaction or treatment-by-centre interaction was tested for any of these secondary variables. A one-sample Wilcoxon signed rank test was used for the analyses of the secondary variables PID, PR score, and global medication performance assessment. All statistical testing was two-tailed using $\alpha=0.05$.

6.1.1.1.9. Participant flow

Figure 2: Study 099-14: Participant flow



a Five of the patients withdrawn during the dose titration period subsequently died. b A total of 80 patients achieved a successful dose during the dose titration period of which 3 patients did not enter the double-blind treatment period. c Two of the 9 patients withdrawn during the double-blind treatment period subsequently died. NOTE: Numbers in parentheses=number of patients.

6.1.1.1.10. Major protocol violations/deviations

During the study, protocol deviations and violations were reported by the investigators for 6 (5%) patients and 3 (2%) patients, respectively. The deviations were noncompliance with study drug administration requirements. During the analysis additional protocol violation were discovered by the sponsor. These protocol violations were mostly related to the baseline around the clock opioid usage and/or not starting with 100 µg Oravescent dose at start of titration. The protocol deviations and violations reported above were considered to have no meaningful impact on the interpretation of the results of the study.

6.1.1.1.11. Baseline data

The 123 patients enrolled in this study were outpatients with cancer and BTP who had an ECOG performance rating ≤2. These patients had a mean age of 58.0 years (range 27 to 87 years), 54% were men; 89% were White, 2% Black and 10% Other, and their mean body mass index (BMI) was 25.9 kg/m^2) (range 16.6 to 47.2 kg/m^2).

6.1.1.1.12. Results for the primary efficacy outcome

Least square (LS) mean (SE) $SPID_{30}$ for the 7 episodes for which Oravescent fentanyl was used was 3.0 (0.12) as compared with 1.8 (0.18) for the 3 episodes for which placebo treatment was used, significantly in favour of Oravescent fentanyl treatment ($p<0.0001$).

Table 3: Study 099-14: Mean Summed Pain Intensity Difference 30 Minutes after Administration of Study Drug ($SPID_{30}$) During the Double-Blind Treatment Period (Full Analysis Set)

Statistic	OVF (N=72)	Placebo (N=72)	p-value[a]
N	72	72	
Mean	3.2	2.0	
SD	2.60	2.21	
Median	2.6	1.3	
Min max	−1.0, 12.7	−1.7, 9.7	
LS mean	3.0	1.8	<0.0001
SE of LS mean	0.12	0.18	

a P-value for the treatment comparison is based on a repeated measures analysis of variance (ANOVA) with treatment, centre, and patient within centre as factors.
SPID=summed pain intensity difference; OVF=Oravescent fentanyl; SD=standard deviation; min=minimum; max=maximum; LS=least squares; SE=standard error.

6.1.1.1.13. Results for other efficacy outcomes

6.1.1.1.13.1. Mean summed pain intensity difference (SPID) 15, 45, and 60 minutes after administration of study drug during the double-blind treatment period

LS mean SPIDs for the 7 episodes for which Oravescent fentanyl was used were significantly different from the LS mean SPIDs for the 3 episodes for which placebo was used at the 15-minute (p=0.0005), and 45- and 60-minute time points (both p<0.0001), in favour of Oravescent fentanyl treatment. The differences between the LS mean SPID values for Oravescent fentanyl and placebo increased over time, being 0.3 at 15 minutes, 1.2 at 30 minutes, 2.7 at 45 minutes, and 4.4 at 60 minutes after administration of study drug. This indicates that Oravescent fentanyl was significantly more effective than placebo as early as 15 minutes and through 60 minutes after study drug administration when used for an episode of BTP.

Table 4: Study 099-14: Mean SPID 15, 45 and 60 minutes after administration of study drug during the double blind treatment period

Variable Statistic	OVF (N=72)	Placebo (N=72)	p-value[a]
Mean $SPID_{15}$ n	72	72	
Mean	0.9	0.6	
SD	1.14	0.94	
Median	0.6	0.3	
Min, max	-0.7, 5.9	-1.3, 3.7	
LS mean	0.8	0.5	0.0005

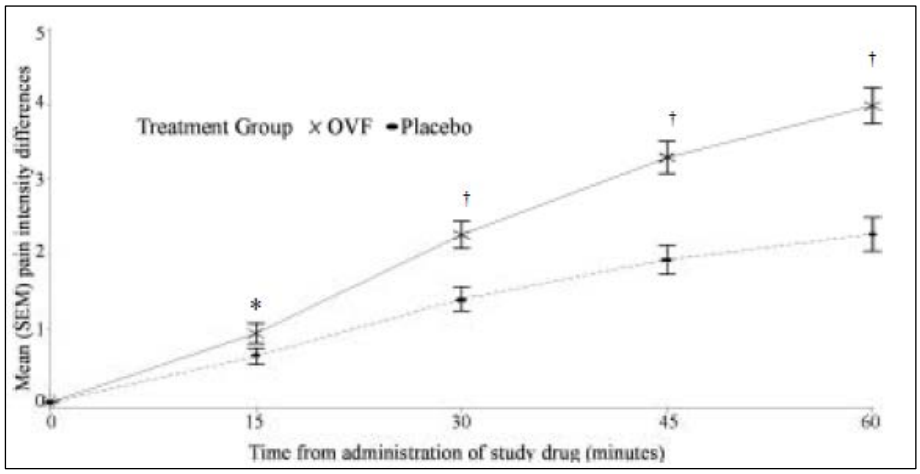
Variable Statistic	OVF (N=72)	Placebo (N=72)	p-value[a]
SE of LS mean	0.06	0.08	
Mean $SPID_{45}$ n	72	72	
Mean	6.5	3.9	
SD	4.23	3.72	
Median	5.3	3.6	
Min, max	-1.1, 20.1	-2.0, 16.3	
LS mean	6.3	3.6	<0.0001
SE of LS mean	0.20	0.30	
Mean $SPID_{60}$ n	72	72	
Mean	10.5	6.2	
SD	5.99	5.49	
Median	8.7	5.4	
Min, max	-1.1, 2 .6	-1.3 23.0	
LS mean	10.2	5.8	<0.0001
SE of LS mean	0.30	0.4	

a P-value for the treatment comparison is based on a repeated measures analysis of variance (ANOVA) with treatment, centre, and patient within centre as factors. OVF=Oravescent fentanyl; SPID=summed pain intensity difference; SD=standard deviation; min=minimum; max=maximum; LS=least squares; SE=standard error.
NOTE: This table does not include the SPID30, which was the primary efficacy variable.

Mean pain intensity difference (PID) at each time point during the double-blind treatment period

The mean PIDs for the 7 episodes for which Oravescent fentanyl was used were statistically significantly different from mean PIDs for the 3 episodes for which placebo was used at the 15-minute (p=0.0029), and 30, 45, and 60 minute time points (all p<0.0001), in favour of Oravescent fentanyl treatment.

Figure 3: Study 099-14: Mean Pain Intensity Difference (PID) at Each Time Point During the Double-Blind Treatment Period (Full Analysis Set)

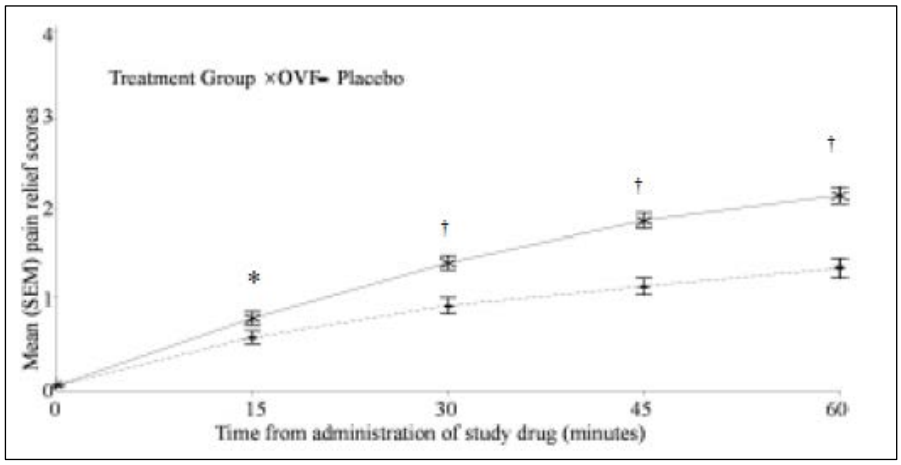


* p<0.01 OVF versus placebo, in favour of OVF, by one-sample Wilcoxon signed rank test. † p<0.0001 OVF versus placebo, in favour of OVF, by one-sample Wilcoxon signed rank test. PID=pain intensity difference; OVF=Oravescent fentanyl; SEM=standard error of the mean.

6.1.1.1.13.2. Mean pain relief (PR) scores at each time point during the double-blind treatment period

Mean PR scores for the 7 episodes for which Oravescent fentanyl was used were significantly different from mean PR scores for the 3 episodes for which placebo was used at the 15-minute (p=0.0005) and 30-, 45, and 60-minute time points (all p<0.0001) in favour of Oravescent fentanyl treatment.

Figure 4: Study 099-14: Mean Pain Relief (PR) Score at Each Time Point during the Double-Blind Treatment Period (Full Analysis Set)



* p<0.001 OVF versus placebo, in favour of OVF, by one-sample Wilcoxon signed rank test. † p<0.0001 OVF versus placebo, in favour of OVF, by one-sample Wilcoxon signed rank test. PR=pain relief; OVF=Oravescent fentanyl; SEM=standard error of the mean.

6.1.1.1.13.3. Mean total pain relief (TOTPAR) scores at each time point during the double-blind treatment period

Mean TOTPAR values for the 7 episodes for which Oravescent fentanyl was used were significantly different from mean TOTPAR values for the 3 episodes for which placebo was used at the 15-minute (p=0.0001) and 30-, 45-, and 60-minute time points (all p<0.0001), in favour of Oravescent fentanyl treatment.

6.1.1.1.13.4. Mean global medication performance assessment during the double-blind treatment pPeriod

Mean global medication performance assessment values for the 7 episodes for which Oravescent fentanyl was used were statistically significantly different from mean global medication performance values for the 3 episodes for which placebo was used at the 30- and 60-minute time points (both p<0.0001), in favour of Oravescent fentanyl treatment.

Table5: Study 099-14: Mean Global Medication Performance Assessment 30 and 60 minutes after Administration of Study Drug during the Double Blind Treatment Period (Full Analysis Set)

Variable Statistic	OVF	Placebo	p-value[a]
Mean GMP assessment at 30 minutes			
n[b]	71	70	
Mean	1.4	0.9	<0.0001
SD	0.84	0.91	
Median	1.1	0.7	
Min, max	0.0, 4.0	0.0, 4.0	
Mean GMP assessment at 60 minutes			
n[b]	70	69	
Mean	2.1	1.3	<0.0001
SD	0.81	1.06	
Median	2.0	1.0	
Min, max	0.2, 4.0	0.0, 4.0	

a P-value for the treatment comparison is based on one-sample Wilcoxon signed rank test. b Number of patients with required assessments, including a baseline pain intensity value. OVF=Oravescent fentanyl; GMP=global medication performance; SD=standard deviation; min=minimum; max=maximum.

6.1.2. Rescue medication use during the double-blind treatment period

Rescue medication was used for 117 (23%) of the 493 BTP episodes for which Oravescent fentanyl was used compared with 105 (50%) of the 208 BTP episodes for which placebo was used in the double-blind treatment period. Conversely, the percentage of BTP episodes for which no rescue medication was used was 76% of episodes for which Oravescent fentanyl was used compared with 50% for which placebo was used in the double-blind treatment period. These data resulted in a relative risk ratio of 0.47, with 95% CI values of 0.37 to 0.60.

6.1.2.1. Time to use of rescue medication by treatment

No inferential statistics were computed for time to use of rescue medication.

Table 6: Study 099-14: Time to use of rescue medication in minutes by treatment (full analysis set)

Variable Statistic	OVF (N=493)	Placebo (N=208)
Time to start of rescue medication		
0 - ≤ 30 minutes	11 (2)	9 (4)
31 - ≤ 45 minutes	15 (3)	19 (9)
46 - ≤ 60 minutes	15 (3)	12 (6)
> 60 minutes	23 (5)	32 (15)
No rescue medication used	376 (76)	103 (50)
No start time available	53 (11)	33 (16)
Time to start of rescue medication		
N	64	72
Mean	57.1	61.5
SD	23.64	26.23
SE of mean	2.96	3.09
Median	55.0	60.0
Min, max	18.0, 122.0	29.0, 138.0

6.1.2.2. Study C25608/3039/BP/US

A Double-Blind, Randomised, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Oravescent® Fentanyl Citrate in Opioid-Tolerant Patients With Cancer and Breakthrough Pain.

6.1.2.2.1. Study design, objectives, locations and dates

A study conducted at 30 sites in the USA from January 2005 to September 2007. The study included an initial open label titration period followed by a double blind, randomised, placebo controlled treatment period.

Primary Objective: To evaluate the efficacy of Oravescent fentanyl compared with placebo in alleviating breakthrough pain (BTP) in opioid tolerant patients with cancer as measured by the time-weighted sum of pain intensity differences (SPID) from 5 through 60 minutes after administration of study drug ($SPID_{60}$).

Secondary objectives:

- To determine the efficacy of Oravescent fentanyl compared with placebo in alleviating BTP as measured by the following:
  - the pain intensity difference (PID) at 5, 10, 15, 30, 45, 60, 90, and 120 minutes after administration of study drug, calculated as the patients' ratings of pain intensity (PI) at

each of these time points minus their rating of PI immediately prior to study drug administration

- the $SPID_{30}$, $SPID_{90}$, and $SPID_{120}$, calculated as the time-weighted sum of the PIDs from 5 through 30 minutes, 5 through 90 minutes, and 5 through 120 minutes, respectively, after administration of study drug
- the patients' assessments of pain relief (PR) at 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug
- the patients' assessments of total pain relief (TOTPAR) through 60, 90, and 120 minutes after administration of study drug ($TOTPAR_{60}$, $TOTPAR_{90}$, and $TOTPAR_{120}$, respectively)
- the time from administration of study drug to the time when meaningful PR of BTP was achieved as measured with a stopwatch
- a global medication performance assessment at 60 and 120 minutes after administration of study drug
- the proportion of episodes in which standard rescue medication after the administration of study drug was required for relief of BTP
- the patients' preferences for BTP medication as evaluated by the patient assessment of study medication

- To determine the safety and tolerability of Oravescent fentanyl treatment in alleviating BTP.

6.1.2.2.2. Inclusion and exclusion criteria

Inclusion: male and female (non-childbearing potential) aged 18 to 80 years who had histologically documented diagnosis of malignant solid tumour or a haematological malignancy causing cancer related pain. Patients had to be opioid tolerant with an average PI score, over the prior 24 hours, of <7 (on 10 point scales) for their persistent cancer pain, and were experiencing, on average 1 to 4 BTP episodes per day while taking around the clock (ATC) opioid therapy and obtained at least partial relief from rescue opioid therapy. Patients had a life expectancy of at least 2 months.

Exclusion: Main exclusion was uncontrolled or rapidly escalating pain as determined by the investigator or any other medical condition or was receiving concomitant medication or therapy that could have compromised the patient's safety, compliance to protocol or data collection.

6.1.2.2.3. Study treatments

In the initial period the patients received open label Oravescent fentanyl tablets to be used to individually determine through titration a successful dose, defined as the dose that provided adequate analgesia (sufficient pain relief within 30 minutes for 2 consecutive BTP episodes). The starting titration dose was selected on the basis of the medications used by the patient for BTP immediately prior to study entry. In the double blind phase the patients were randomised to a sequence of 10 blinded study drug treatments (7 Oravescent fentanyl tablets at the successful dose and 3 matching placebo tablets in a prespecified sequence).

6.1.2.2.4. Efficacy variables and outcomes

The primary efficacy outcome was the $SPID_{60}$ for each BTP episode during the double-blind treatment period.

The $SPID_{60}$ was calculated using the data collected on the patient's diary and was derived from the time-weighted sum of the PID scores recorded 5, 10, 15, 30, 45, and 60 minutes after the administration of study drug.

PI scores were assessed by the patient on an 11-point numerical rating scale from 0=no pain to 10=worst pain, immediately prior to the administration of study drug and 5, 10, 15, 30, 45, and

60 minutes after the administration of study drug for each episode of BTP and were recorded in the patient's electronic diary.

The PID is the difference between the PI scores immediately prior to and 5, 10, 15, 30, 45, and 60 minutes after the administration of study drug.

Other efficacy outcomes included:

- Sum of the Pain Intensity Differences - The $SPID_{30}$, $SPID_{90}$, and $SPID_{120}$ scores were calculated as the sum of the PID scores from 5 through 30 minutes, 5 through 90 minutes, and 5 through 120 minutes, respectively, after the administration of study drug
- Pain Intensity Difference - The PID was calculated for 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug. The PID was calculated as the patients' ratings of PI at each of these time points minus the rating of PI immediately before the administration of study drug
- Pain Relief - The PR scores 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug were recorded on the patient's diary. The PR scores were assessed using a 5-point Likert scale (0=none to 4=complete)
- Total Pain Relief - The $TOTPAR_{60}$, $TOTPAR_{90}$, and $TOTPAR_{120}$ scores were calculated as the sum of PR scores recorded 5 through 60 minutes, 5 through 90 minutes, and 5 through 120 minutes, respectively, after the administration of study drug
- Time to Meaningful Pain Relief - The time in minutes to when meaningful pain relief was achieved after the administration of study drug was recorded in the patient's diary
- Global Medication Performance Assessment - The global medication performance assessment was recorded in the patient's diary at 60 and 120 minutes after the administration of study drug (and immediately before the use of any rescue medication for any episode of BTP for which rescue medication was used). Patients rated how well each dose of study drug performed in controlling BTP using a 5-point scale (0=poor through 4=excellent)
- Use of Standard Rescue Medication - Any use of standard rescue medication after the administration of study drug was recorded in the patient's diary.

6.1.2.2.5. Randomisation and blinding methods

The treatment during the dose titration period was open-label. For treatment during the double-blind treatment period, each patient was randomly assigned to a sequence of 10 tablets, consisting of 7 active tablets of the successful dose strength established during the dose titration period and 3 matching placebo tablets. Thus, patients served as their own controls in the efficacy analyses of results in the double-blind treatment period. Both the investigators and patients were blinded to the treatment-sequence assignments.

6.1.2.2.6. Analysis populations

Safety analysis set includes those patients in the set of enrolled patients who took 1 or more doses of study drug during the dose titration period of the study.

Full analysis set includes those patients in the double-blind safety analysis set who took Oravescent fentanyl for at least 1 BTP episode and took placebo for at least 1 BTP episode, according to the actual treatment received, during the double-blind treatment period, and have a pretreatment pain intensity score for each of these episodes.

Evaluable analysis set included those evaluable patients in the full analysis set who took Oravescent fentanyl for at least 1 evaluable BTP episode and took placebo for at least 1 evaluable BTP episode, according to the actual treatment received, during the double-blind treatment period.

6.1.2.2.7. Sample size

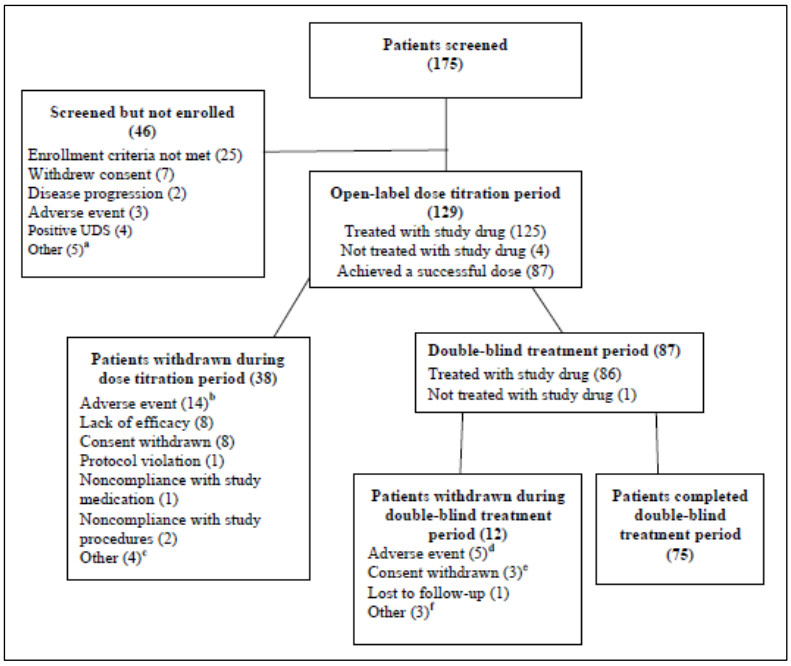
For this sample size calculation, a treatment difference of 3.00 in $SPID_{60}$ was considered clinically relevant. Results from a double-blind, placebo-controlled study with oral transmucosal fentanyl citrate in patients with cancer and BTP were used to estimate the sample size for this study. Using the data from this study, the SD of the treatment difference was estimated as 7.58. This value is the upper 95% confidence limit of the estimate of the SD for the treatment difference of 6.44. This estimate of the SD yielded a power of 90% for 70 evaluable patients (1-sample t-test, alpha=5%, 2-sided). Assuming that 10% of randomised patients would not be evaluable for efficacy, approximately 80 patients were to be randomised. Previous studies indicated that between 20% and 40% of patients withdrew during the dose titration period of the study; therefore, a total of up to approximately 140 patients were to be enrolled into the open-label dose titration period of the study.

6.1.2.2.8. Statistical methods

The primary analysis was tested using an analysis of variance (ANOVA) with treatment as a fixed effect and patient as a random effect. The statistical test was 2-tailed using α =0.05. A permutation test was performed on the primary variable to assess robustness of the results. For this purpose, the patients' data used in the primary analysis were reassigned to the 18 treatment sequences randomly. The permutation distribution is formed by ignoring the blocks and randomly reassigning the patients to the various treatment sequences. The test statistic is the sum of the observations with the placebo label. A significant treatment effect is detected if less than 5% of the test statistic based on the permutation data is smaller than the observed value. The observed test statistic value, the proportion of the test statistic based on permutation less than the observed value, and the number of replications performed are summarised. The model for the primary efficacy analysis was also the model for the secondary variables of SPID, PID, and TOTPAR. A 1-sample Wilcoxon signed rank test was used, based on average scores for each patient per treatment, to test the differences between the 2 treatments for the analyses of the secondary variables PR score and global medication performance assessment. All statistical testing for secondary variables was 2-tailed using α=0.05. No adjustment was made for multiplicity.

6.1.2.2.9. Participant flow

Figure 5: Study 3039: Participant flow



a 1 patient went to hospice, 1 had surgery, 1 died, 1 was medically unstable because of a worsening infection, and 1 was not included for unknown reasons. b Includes 2 patients who subsequently died. c 4 patients were withdrawn during the titration period for reason of "other" as follows: 2 patients did not experience BTP; 1 patient was not compliant with other prescription medication and therefore was no longer considered reliable; and 1 patient had a history of alcohol abuse reported by his spouse. d Includes 2 patients who subsequently died. e Includes 1 patient who was randomised but not treated. f 3 patients were withdrawn during the double-blind treatment period for reason of "other"; 3 patients stopped experiencing BTP episodes after randomisation. UDS=urine drug screen for the presence of drugs prohibited by the protocol. NOTE: Numbers in parentheses=number of patients.

6.1.2.2.10. Major protocol violations/deviations

The commonest protocol violation was patients not meeting the inclusion/exclusion criteria and several were given exemptions to enter the trial despite this (usually for presence of sleep apnoea) and for having baseline pain above entry criteria. One patient was withdrawn from the study due to positive drug screen for cocaine not received until after randomisation. The total number of violations was low and were considered to have no meaningful impact on the results of the study.

6.1.2.2.11. Baseline data

For the 129 patients enrolled into the study the mean age was 54.9 years (range 29 to 79 years), 62% were women, 82% of the patients were white, 8% black and 10% "other", and their mean BMI was 27.9 kg/m^2 (range 11.6 to 53.1 kg/m^2). The analgesics used most commonly as rescue medication were oxycodone/acetaminophen (31 patients, 25%), hydrocodone/acetaminophen (25 patients, 20%), and oxycodone (23 patients, 18%). At baseline, the mean oral morphine equivalent dose per day taken as ATC medication was 279.2 mg (range 60 to 3198 mg), and the mean oral morphine equivalent dose per day taken as rescue medication for BTP was 24.7 mg (range 4 to 480 mg) per episode.

6.1.2.2.12. Results for the primary efficacy outcome

6.1.2.2.12.1. Summed pain Intensity difference at 60 minutes

The primary efficacy variable, the SPID assessed at 60 minutes after administration of study drug, showed a statistically significant (p<0.0001) difference between Oravescent fentanyl and placebo treatment in favour of Oravescent fentanyl.

Table 7: Study 3039: Mean Summed Pain Intensity Difference 60 Minutes Post treatment (Full Analysis Set)

Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
Mean SPID 60 minutes post treatment				
N	78	78		
Mean	9.7	4.9		
SD	5.58	4.38		
SE of mean	0.63	0.50		
Median	8.9	4.2		
Min, max	0.0, 26.8	-0.9, 21.8		

Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
LS mean	9.8	5.0	<0.0001	3.87, 5.64
SE of LS mean	0.26	0.38		

a The confidence interval is the difference between the 2 treatment groups (OVF-placebo).

CI=confidence interval; min=minimum; max=maximum, OVF=Oravescent fentanyl; LS=least squares; SD=standard deviation; SE=standard error; SPID=sum of pain intensity differences.

NOTE: The LS mean, SE of LS mean, and the p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual BTP episodes with treatment as a fixed factor and patient as a random factor.

A permutation test for SPID at 60 minutes was performed twice, once for all patients in the full analysis set and once for those patients in the full analysis set with 10 BTP episodes. Ten-thousand replications were performed for each test. For both tests, less than 0.0001 of the test statistic is smaller than the observed value, indicating a significant treatment effect which confirms the primary efficacy results.

6.1.2.2.13. Results for other efficacy outcomes

6.1.2.2.13.1. Mean summed pain intensity difference 30, 90, and 120 minutes after study drug administration

The SPIDs 30, 90, and 120 minutes after study drug administration ($SPID_{30}$, $SPID_{90}$, and $SPID_{120}$) each showed a statistically significant (p<0.0001) difference between Oravescent fentanyl and placebo treatment in favour of Oravescent fentanyl.

Table 8: Study 3039: Mean summed pain intensity differences at 30, 90, and 120 minutes post treatment (full analysis set)

Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
Mean $SPID_{30}$ minutes post treatment				
N	78	78		
Mean	3.3	1.8		
SD	2.23	1.92		
SE of mean	0.25	0.22		
Median	2.7	1.3		
Min, max	0.0, 9.6	-0.6, 9.8		
LS mean	3.3	1.9	<0.0001	1.07, 1.80
SE of LS mean	0.11	0.16		

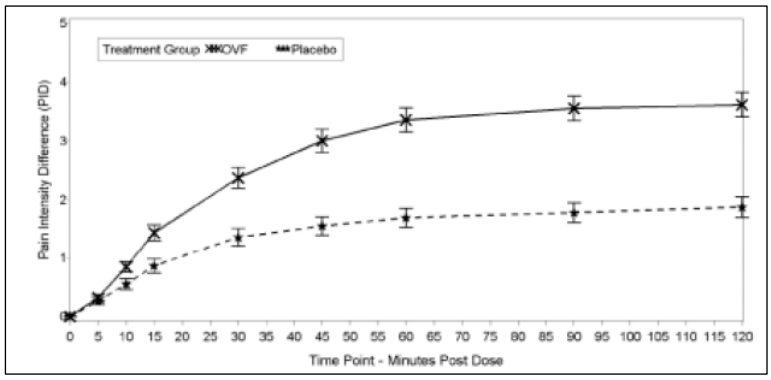
Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
Mean $SPID_{90}$ minutes post treatment				
N	78	78		
Mean	16.9	8.4		
SD	9.03	6.99		
SE of mean	1.02	0.79		
Median	15.2	7.6		
Min, max	0.7, 44.0	-2.3, 33.8		
LS mean	17.0	8.5	<0.0001	7.04, 9.92
SE of LS mean	0.42	0.62		
Mean $SPID_{120}$ minutes post treatment				
N	78	78		
Mean	24.2	12.0		
SD	12.58	9.75		
SE of mean	1.42	1.10		
Median	22.4	10.8		
Min, max	1.3, 60.5	-4.3, 45.8		
LS mean	24.3	12.1	<0.0001	10.17, 14.20
SE of LS mean	0.59	0.86		

a The confidence interval is the difference between the 2 treatment groups (OVF-placebo). SPID=sum of pain intensity differences; OVF=Oravescent fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum; LS=least squares; CI=confidence interval. NOTE: The LS mean, SE of LS mean, and the p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual BTP episodes with treatment as a fixed factor and patient as a random factor.

6.1.2.2.13.2. Pain intensity difference

The mean PI (6.4) was the same before use of Oravescent fentanyl for a BTP episode and before use of placebo for a BTP episode. At 10 minutes and at all time points through the end of the observation period (120 minutes), there was a statistically significant difference (p<0.0001) in favour of treatment with Oravescent fentanyl. The treatment effect increased through 1 hour and was maintained through 2 hours.

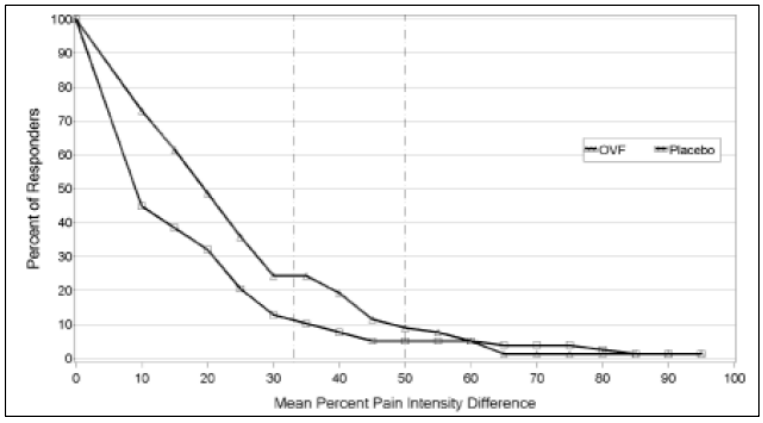
Figure 6: Study 3039: Mean (±SEM) Pain Intensity Difference at Each Time Point by Treatment Received (Full Analysis Set)



SEM=standard error of the mean; OVF= Oravescent fentanyl.

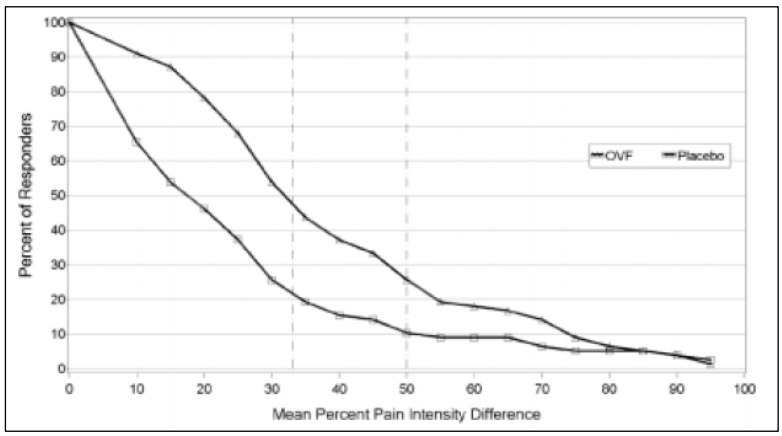
6.1.2.2.13.3. Cumulative Response (by Patient)

Figure 7: Study 3039: Cumulative Proportion of Patients-Responder Analysis 15 Minutes Post treatment (Full Analysis Set)



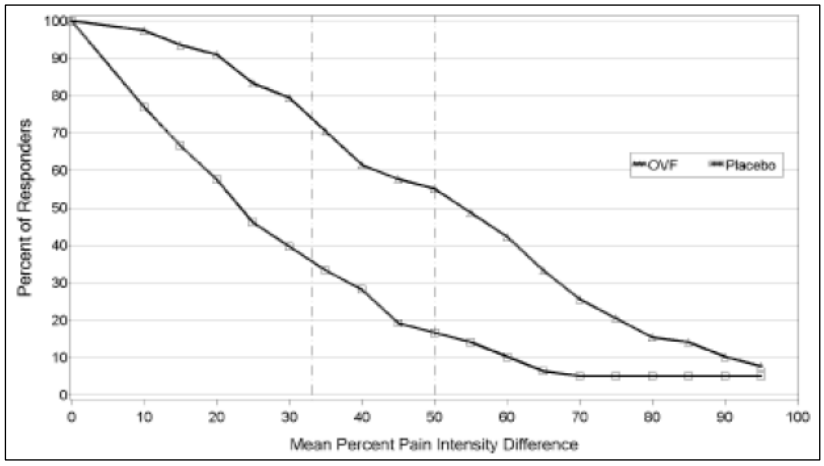
OVF = Oravescent

Figure 8: Study 3039: Cumulative Proportion of Patients-Responder Analysis 30 Minutes Post treatment (Full Analysis Set)



OVF = Oravescent

Figure 9: Study 3039: Cumulative Proportion of Patients-Responder Analysis 60 Minutes Post treatment (Full Analysis Set)



OVF = Oravescent

6.1.2.2.13.4. Clinically meaningful response (by Episode)

Statistically significant separation between the treatments in the proportion of episodes where a given level of improvement was achieved was seen as early as 10 minutes for at least 33% improvement and for at least 50% improvement.

Table 9: Study 3039: Episodes with at least 33% and 50% improvement in pain intensity from baseline at each time point (episodes for the full analysis set)

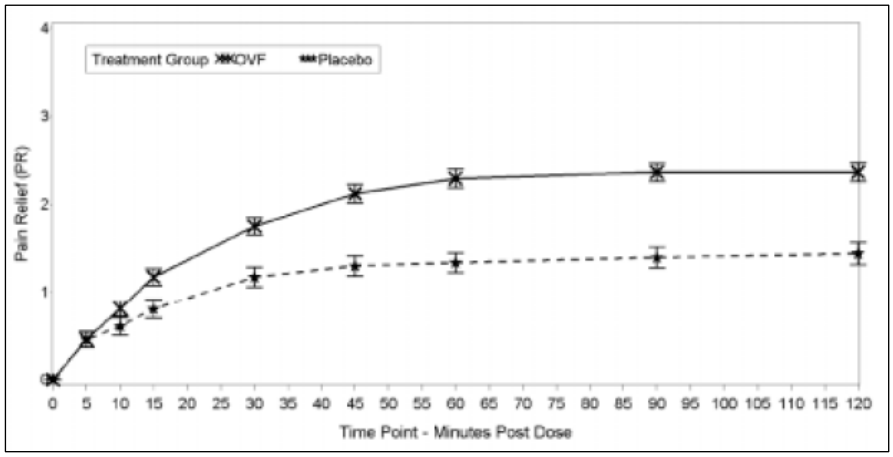
Time Post treatment (minutes)	Number (%) of episodes with ≥33% pain intensity improvement			Number (%) of episodes with ≥50% pain intensity improvement		
	OVF (N=493)	Placebo (N=223)	p-value[a]	OVF (N=493)	Placebo (N=223)	p-value[a]
5	23 (5)	6 (3)	0.1200	9 (2)	4 (2)	0.9436
10	77 (16)	23 (10)	0.0072	34 (7)	9 (4)	0.0332
15	145 (29)	32 (14)	<0.0001	89 (18)	18 (8)	<0.0001
30	253 (51)	58 (26)	<0.0001	186 (38)	34 (15)	<0.0001
45	319 (65)	70 (31)	<0.0001	259 (53)	44 (20)	<0.0001
60	342 (69)	73 (33)	<0.0001	292 (59)	50 (22)	<0.0001
9	360 (73)	80 (36)	<0.0001	313 (63)	58 (26)	<0.0001
120	363 (74)	85 (38)	<0.0001	324 (66)	62 (28)	<0.0001

a The analysis is based on a Generalized Estimating Equation (GEE) model with a logit link function adjusted for intrapatient correlation. OVF=Oravescent fentanyl.

6.1.2.2.13.5. Patient assessments of pain relief

After 5 minutes, mean PR was similar for episodes for which the patient took Oravescent fentanyl and for episodes for which the patient took placebo. Mean PR showed a statistically significant (p<0.0001) difference between Oravescent fentanyl and placebo treatment in favour of Oravescent fentanyl after 10 minutes and at all subsequent time points. Pain relief increased through 1 hour after the administration of study drug and was maintained through 2 hours.

Figure 10: Study 3039: Mean (±SEM) Pain Relief at Each Time Point by Treatment Received (Full Analysis Set)



SEM=standard error of the mean; OVF=Oravescent fentanyl

6.1.2.2.13.6. Patients' assessments of total pain relief

TOTPAR was statistically significantly (p<0.0001) greater at every time point for episodes for which the patient took Oravescent fentanyl than for episodes for which the patient took placebo.

Table 10: Study 3039: Mean total pain relief scores at each time point (full analysis set)

Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
Mean TOTPAR after 60 minutes				
N	78	78		
Mean	7.0	4.4		
SD	3.12	3.57		
SE of mean	0.35	0.40		
Median	6.3	3.8		
Min, max	1.3, 16.0	0.0, 16.0		
LS mean	7.1	4.3	<0.0001	2.21, 3.28
SE of LS mean	0.16	0.23		
Mean TOTPAR after 90 minutes				
N	78	78		

Variable Statistic	OVF (N=78)	Placebo (N=78)	p-value	95% CI[a]
Mean	11.8	7.1		
SD	4.74	5.54		
SE of mean	0.54	0.63		
Median	11.3	6.4		
Min, max	2.7, 24.0	0.0, 24.0		
LS mean	11.9	7.0	<0.0001	3.95, 5.70
SE of LS mean	0.26	0.37		
Mean TOTPAR after 120 minutes				
N	78	78		
Mean	16.5	10.0		
SD	6.44	7.60		
SE of mean	0.73	0.86		
Median	15.5	9.7		
Min, max	4.0, 32.0	0.0, 32.0		
LS mean	16.6	9.8	<0.0001	5.61, 8.05
SE of LS mean	0.36	0.52		

a The confidence interval is the difference between the 2 treatment groups (OVF-placebo). TOTPAR=total pain relief; OVF=Oravescent fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum, LS=least squares; CI=confidence interval. NOTE: The LS mean, SE of LS mean, and the p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual BTP episodes with treatment as a fixed factor and patient as a random factor.

6.1.2.2.13.7. Meaningful pain relief

Meaningful pain relief was experienced for 32% (158 of 493) of episodes for which the patient took Oravescent fentanyl compared to 13% (29 of 223) of episodes for which the patient took placebo. These data resulted in a relative risk ratio of 3.26, with 95% CI values of 1.97 to 5.40. This finding means that patients were approximately 3.26 times more likely to achieve meaningful pain relief from a BTP episode while taking Oravescent fentanyl than while taking placebo.

6.1.2.2.13.8. Global medication performance assessment

Global medication performance was assessed by patients 60 and 120 minutes after the administration of study drug. The mean difference in performance between the 2 treatments was statistically significant (p<0.0001) in favour of Oravescent fentanyl at both time points.

Table 11: Study 3039: Mean global medication performance assessment at each time point during the double blind treatment period by treatment received (full analysis set)

Variable Statistic	OVF (N=78)	Placebo (N=78)	P value[a]	95% CI[b]
Performance assessment after 60 minutes				
N	78	78		
Mean	2.1	1.2	<0.0001	0.83, 4.00
SD	0.90	1.03		
SE of mean	0.10	0.12		
Median	2.0	1.0		
Min, max	0.6, 4.0	0.0, 4.0		
Performance assessment after 120 minutes				
N	78	76		
Mean	2.3	1.2	<0.0001	0.90, 3.86
SD	0.87	1.01		
SE of mean	0.10	0.12		
Median	2.2	1.3		
Min, max	0.3, 4.0	0.0, 4.0		

a The p-value for the treatment comparison is from a 1-sample Wilcoxon signed rank test. b The confidence interval is the difference between the 2 treatment groups (OVF-placebo). OVF=Oravescent fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum.

6.1.2.2.13.9. Patient preferences for breakthrough pain medication

The patient preferences for BTP medication were assessed by the Patient Assessment of Study Medication questionnaire at end of double blind treatment (or early withdrawal). The majority (72%) of patients rated the study medication superior to the medication used for BTP prior to study entry in faster onset of pain relief. In addition with regard to the study medication, 79% rated onset of action good or excellent; 73% rated ease of administration good or excellent; and 79% rated convenience of use as good or excellent. The majority (53%) of patients preferred the study medication to their prior rescue medication.

6.1.2.2.13.10. Rescue medication use during the double-blind treatment period

Rescue medication was used for 53 (11%) of the 493 BTP episodes for which Oravescent fentanyl was used compared with 67 (30%) of the 223 BTP episodes for which placebo was used in the double-blind treatment period. Expressing these data conversely, the percentage of BTP episodes for which no rescue medication was used was 89% of episodes for which

Oravescent fentanyl was used compared with 70% of episodes for which placebo was used in the double-blind treatment period. These data resulted in a relative risk ratio of 3.58, with 95% CI values of 2.23 to 5.75. This finding means that patients were approximately 3.58 times as likely to use rescue medication for a BTP episode for which placebo had initially been used than for a BTP episode for which Oravescent fentanyl had initially been used.

Table 12: Study 3039: Standard Rescue medication use by treatment during the double blind treatment period (Episodes for the full analysis set)

	Episodes treated, n (%)			Relative risk[a]	
	OVF (N=493)	Placebo (N=223)	Total (N=716)	Odds ratio (placebo vs OVF)	95% CI
Rescue medication used	53 (11)	67 (30)	120 (17)	3.58	2.23, 5.75

a The odds ratio was obtained using a Generalized Estimating Equation (GEE) model with a logit link function adjusted for intrapatient correlation. OVF = Oravescent

6.1.3. Other efficacy studies

6.1.3.1. Study C25608/4027/BP/EU

A European Multicentre Open Label Study of Breakthrough Cancer Pain: Assessment of Fentanyl Buccal Tablets Titration and Treatment in Opioid Tolerant.

6.1.3.1.1. Study design, objectives, locations and dates

The study was conducted at 135 centres in 7 European countries: France (22 centres), Germany (32), Spain (28), Ireland (2), Italy (26), Poland (18) and UK (7) from January 2009 to May 2011. The study included an open label titration period in which patients were randomised to receive a starting dose of 100 µg (Group A) or 200 µg (Group B). Patients were then individually titrated to an effective FBT dose. Once the effective dose had been identified the patients entered an open label treatment period in which each patients treated 8 episodes of FBT. Once patients completed the 8 episodes they had to option to continue treatment in an open label continuation period which continued until the product became commercially available.

Primary objective:

To compare the percentage of patients reaching an effective FEBT dose with a starting dose of 100 µg to those with a starting dose of 200 µg.

Secondary objectives:

- to evaluate the safety and tolerability of FEBT treatment for breakthrough pain (BTP)
- to evaluate the analgesic efficacy of FEBT 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.

6.1.3.1.1.1. Study population

Male and female (non-childbearing potential) patients aged at least 18 years with histologically documented diagnosis of cancer and experiencing up to 4 BTP episodes per 24 hours (on

average) with on stable background pain opioid treatment of at least 60 mg of oral morphine/day, or at least 25 µg of transdermal fentanyl/hour, or at least 30 mg of oxycodone/day, or at least 8 mg of hydromorphone/day, or an equianalgesic dose of another opioid for a week or longer before administration of the first dose of study drug.

Patients were excluded if they had uncontrolled or rapidly escalating pain as determined by the investigator or they had respiratory depression or chronic obstructive pulmonary disease, or any other medical condition predisposing to respiratory depression or they had any medical or psychiatric disease that, in the opinion of the investigator, would compromise collected data.

6.1.3.1.1.2. Study treatments

During the open-label dose titration period, patients used 1 to 4 tablets at the 100 µg or 200 µg strengths to titrate FEBT. For the open-label treatment period, single dose tablets at the effective dose strength were used. FEBTs were placed above a rear molar tooth between the upper gum and cheek (buccally) (not above an incisor tooth). The tablet was left between the cheek and gum until dissolved, which usually took approximately 14 to 25 minutes. After 30 minutes, if pieces of tablet remained, the patient swallowed with water.

Table 13: Study 4027: Titration schema

	Titration group A		Titration group B	
	First dose[a]	Second dose[b]	First dose[a]	Second dose[b]
First BTP episode	100 µg	100 µg	200 µg[c]	200 µg
Second BTP episode	200 µg	200 µg	400 µg	200 µg
Third BTP episode	400 µg	200 µg	600 µg	200 µg
Fourth BTP episode	600 µg	200 µg	800 µg	-
Fifth BTP episode	800 µg[d]	-	-	-

a If the first dose was effective, the effectiveness of the dose was to be confirmed during the following BTP episode. b If the second dose was needed after 30 minutes. c The dose may have been titrated-down to 100 mcg if 200 mcg was not acceptable. d If this dose was not the effective dose, the patient was to be withdrawn from the study. BTP=breakthrough pain. NOTES: Titrate-up to 800 mcg was only necessary if none of the lower first doses was determined as effective dose.

6.1.3.1.1.3. Efficacy outcomes

- percentage of patients reaching an effective dose by titration (primary outcome – comparison of Group A and Group B in titration period)
- time to meaningful pain relief (recorded by stopwatch)
- use of standard rescue medication.

6.1.3.1.1.4. Statistical methods

Given the titration success rate of 65% seen in previous studies, a total of 880 patients (440 per group) were needed to have 80% power to demonstrate the non-inferiority of starting with a 200 µg dose rather than a 100 µg dose (based on the large sample normal approximation test of proportions with a one sided 0.050 significance level).

The primary efficacy variable, namely achieving an effective dose, was analysed by estimating the effective dose rate (i.e., number of patients reaching an effective dose divided by the total number of patients in the titration group) in each randomised titration group and comparing

the confidence interval (CI) for the difference, calculated as 100 mcg – 200 mcg, with the non-inferiority margin. In order to assess if non-inferiority was met (ie, whether the null hypothesis was rejected), a two-sided 90% CI equivalent to a one-sided 95% CI was calculated. Non-inferiority was established if the upper bound of the two-sided CI was less than 8%. Kaplan-Meier analysis was used to estimate the distribution of time to meaningful pain relief overall (the total number of episodes) and average (taken to be the average time for each patient to achieve meaningful pain relief). Secondary efficacy data were summarised with descriptive statistics.

6.1.3.1.1.5. Participant flow

Total screened = 442

Total enrolled = 330

Randomised to Group A (100 µg) = 156

Randomised to Group B (200 µg) = 174

Total enrolled and randomised and received at least one dose = 312 (titration safety analysis set)

Total entered treatment phase = 281

Total completed treatment phase = 218

Total entered continuation phase = 166

Comment: It is noted that enrolment is lower than that planned. It is stated that this was due to recruitment problems but many patients (99) were screened and not enrolled due to "study drug not dispensed" – this is not explained.

6.1.3.1.1.6. Baseline data

The titration groups (100 µg titration group and 200 µg titration group) were well matched in regard to age (mean 59.5 and 60.1 years, respectively), sex (54.5% and 55.2% men, respectively), and weight (mean 67.54 and 71.54 kg, respectively). Baseline characteristics for cancer history, persistent cancer pain, BTP assessment, physical examination and oral mucosal examination were generally similar between patients in both titration groups.

6.1.3.1.1.7. Results for the primary efficacy outcome

The effective dose rate (number of patients reaching an effective dose divided by the total number of patients in the titration group) was slightly lower for patients in the 100 µg titration group (75.2%) compared to patients in the 200 µg titration group (81.4%), which provided a treatment comparison difference of -6.3%. despite the loss of power due to the reduced sample size a two-sided 90% CI for the difference in effective dose rates (calculated as 100 µg - 200 µg) was constructed and an upper limit of 1.4% was obtained. Non-inferiority was established if the upper limit of the CI was <8%, therefore with an upper limit of 1.4%, non-inferiority was established.

Table 14: Study 4027: Primary Efficacy Analysis: Effective Dose as Assessed by the Patient by Randomised Titration Group (Titration Safety Analysis Set)

Variable Statistic	100 µg group (N=145)	200 µg group (N=167)
Number of patients with a response, n (%)	124 (85.5)	149 (89.2)
Reached effective dose, n (%)	109 (87.9)	136 (91.3)
Did not reach effective dose, n (%)	15 (12.1)	13 (8.7)
Missing	21	18
Effective dose rate, %	75.2	81.4
Treatment comparison:		
Effective dose rate, % (100 µg – 200 µg)		-6.3
Upper limit of 90% CI[a]		1.4

a Upper limit of the 2-sided 90% CI for the difference in the effective dose rate of 100 µg – 200 µg.
CI=confidence interval; n=number of patients with a response; N=number of patients in specified analysis set and group. NOTES: Percentages for the number of patients with a response and the effective dose rate are based on N. Other percentages are based on the number of patients with a response. Non-inferiority was established if the upper limit of the CI was <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 µg (39.6% of patients), and 400 µg (26.9% of patients). The most frequently reported effective dose of study drug for both titration groups was 200 µg (33.9% and 44.1% for the 100 µg titration group and 200 µg titration group, respectively), whereas the 100 µg dose was reported as the effective dose of study drug for 31.2% of patients in the 100 µg titration group and 5.1% of patients in the 200 µg titration group, and the 400 µg dose was reported as the effective dose of study drug for 22.0% of patients in the 100 µg titration group and 30.9% of patients in the 200 µg titration group.

6.1.3.2. Results for other efficacy outcomes

6.1.3.2.1. 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.

6.1.3.2.2. Use of standard rescue medication

There were 2610 episodes of BTP in the titration period (when looking for an effective dose of FEBT), 3.9% of which required rescue medication. There were 1810 episodes of BTP in the treatment period, 8.5% of which required rescue medication.

6.1.3.2.3. Medication performance assessment

Medication performance was assessed at 30 and 60 minutes after the administration of study drug during the treatment period (day 1 to day 8 and over all episodes). For each episode, the

patient answered the question 'How well did your study medication perform in controlling the breakthrough pain episode?' on a 5-point Likert-type scale (poor=0, fair=1, good=2, very good=3, and excellent=4).

At all time points (day 1 to day 8), a 'good' response was the most frequent response at 30 minutes after medication and a 'good' or 'very good' response was the most frequent response at 60 minutes after medication.

Table 15: Study 4027: Medication Performance Assessment 30 and 60 Minutes after Medication Over All Episodes (Safety Analysis Set)

Scale, n (%)	Minutes after medication (N=223)	
	30 Minutes	60 Minutes
Number of patients with a response	222 (99.6)	214 (96.0)
Number of episodes	1776	1668
Excellent	103 (5.8)	144 (8.6)
Very good	433 (24.4)	584 (35.0)
Good	712 (40.1)	646 (38.7)
Fair	428 (24.1)	245 (14.7)
Poor	100 (5.6)	49 (2.9)
Missing	35	143

n=number of patients with a response; N=number of patients in the specified analysis set. NOTES: Percentages for the number of patients with a response are based on N and the percentages for medication assessments are based on the number of episodes. Medication performance assessment was assessed during the treatment period. Responses represent the answers to the question "How well did your study medication perform in controlling this breakthrough pain episode?"

6.1.3.2.4. 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 favourable effect of the study drug on the patient's quality of life.

6.1.3.2.5. Global assessment by the patient

The patient's global assessment evaluated Patient Satisfaction, Ease of Use, and Patient's Global Impression of Change (PGIC). For Patient Satisfaction, the patients' responses to all questions were rated higher at the end of the treatment period compared to baseline. 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 in 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.

6.1.3.3. Study 099-15

A Multicentre, Open-Label, Long-Term Study of Oravescent® Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients.

6.1.3.3.1. Study design, objectives, locations and dates

A study conducted at 47 centres in the USA from April 2004 to November 2006. The study was open to new patients but also enrolled patients who had completed **Studies 099-14** or **3039**. For new patients there was an open label titration period and then all patients were treated with their individual effective dose for 12 months after which they could continue in the study for ongoing treatment until November 2006 when the product became commercially available in the USA.

Primary objective: To determine the tolerability and safety of Oravescent fentanyl when used long term to relieve pain (BTP) in opioid tolerant patients with cancer.

Secondary objective: To assess the effectiveness of Oravescent fentanyl and the development of incremental tolerance when used long term to treat BTP in opioid tolerant patients who were receiving maintenance opioids.

6.1.3.3.1.1. Study population

Patients could be included in the study if they had successfully completed Studies 099-14 or 3039. New patients had the same inclusion criteria as those studies (ie male or female patients at least 18 years of age who had cancer and who were on a maintenance regimen of opioid analgesics but continuing to experience 1-4 episodes/day of BTP alleviated by a stable dose of fast acting opioid rescue medication. Patients were excluded from the study if they had sleep apnoea or active brain metastases; raised intracranial pressure; COAD characterised by CO_2 retention; renal or hepatic tests at baseline outside prespecified limits; or were at risk of significant bradyarrhythmia because of underlying heart disease.

6.1.3.3.1.2. Study treatments

Roll over patients continued on the effective dose of Oravescent used in the previous studies. New patients entered a 21 day dose titration period starting at 100 µg to determine the individually effective dose. Once the effective dose was determined the patients were dispensed sufficient of the effective dose of Oravescent for 1 month's treatment. Patients returned to the clinic each month for assessment and new supplies.

6.1.3.3.1.3. Efficacy outcomes

- global medication performance assessment
- patient responses to study medication assessment questionnaires

The Global Medication Performance Assessment was assessed on a 5 point scale (0=poor, 1=fair, 2=good, 3=very good, 4=excellent). The patients completed the assessment only once per day.

6.1.3.3.1.4. Statistical methods

Global medication performance assessment is a subjective measure of the effectiveness of the study drug for dealing with the patients' pain. Patients assessed study drug performance daily during the long-term maintenance treatment period. Average patient responses for each visit were summarised using descriptive statistics. Patients' responses to study medication assessment questionnaires were summarised using descriptive statistics for categorical response.

6.1.3.3.1.5. Participant flow

232 patients were enrolled and evaluated for safety, 112 of whom entered the dose titration period (titration safety analysis set) and 120 additional patients who had completed previous double-blind Studies 099-14 or 3039.

The mean duration of exposure overall (ie, during both the dose titration and long-term maintenance treatment period) was 158.4 days (median 99.0 days). There was a wide range (1-698.0 days) in duration of exposure; the majority of patients (53%) received study drug treatment for more than 3 months.

6.1.3.3.1.6. Baseline data

The mean age at study entry was 55.3 years (range 24 to 95 years); 53% women 47% male; 84% were White, 7% Black, 1% Asian, and 1 (<1% Pacific Islander) and 7% "other" (Hispanic and Native American); the mean BMI was 26.7 kg/m^2 (range 14.5 to 53.2 kg/m^2).

At baseline, the ATC opioids used most frequently (10% or more of patients) were transdermal fentanyl (38%), oxycodone (31%), and morphine (21%). The rescue medications used most frequently were hydrocodone/acetaminophen (24%), oxycodone (22%), morphine (15%), oxycodone/acetaminophen (14%), and hydromorphone (12%)

6.1.3.3.2. Results for the efficacy outcomes

6.1.3.3.2.1. Global medication performance assessment

The global medication performance assessments were similar at all visits. They were 2.4 on a scale of 0 to 4 at the start of the maintenance treatment period and 2.1 at the endpoint.

Table 16: Study 099-15: Mean Global Medication Performance Assessment at Baseline and Endpoint (Maintenance Safety Analysis Set)

Time point	n	Mean	SD	Median	Min, max
Start of maintenance (visit 1)	187	2.4	0.87	2.3	0.0, 4.0
Month 1	149	2.5	0.85	2.6	0.0, 4.0
Month 2	135	2.4	0.87	2.2	0.0, 4.0
Month 3	114	2.4	0.88	2.1	0.1, 4.0
Month 4	105	2.3	0.93	2.0	0.1, 4.0
Month 5	90	2.4	0.88	2.1	0.0, 4.0
Month 6	79	2.3	0.92	2.0	0.0, 4.0
Month 7	68	2.3	0.93	2.0	0.0, 4.0
Month 8	64	2.4	0.97	2.1	0.1, 4.0
Month 9	56	2.4	0.95	2.2	0.1, 4.0
Month 10	51	2.3	0.93	2.1	0.0, 4.0
Month 11	46	2.3	0.95	2.0	0.0, 4.0
Month 12	24	2.5	1.00	2.5	0.9, 4.0
Month 13	23	2.4	0.91	2.0	0.8, 4.0

Time point	n	Mean	SD	Median	Min, max
Month 14	22	2.4	0.77	2.0	1.4, 4.0
Month 15	18	2.2	0.79	2.0	1.1, 3.7
Month 16	16	2.3	0.69	2.0	1.6, 3.7
Month 17	12	2.0	0.73	2.0	0.7, 3.0
Month 18	10	2.1	0.57	2.0	1.3, 3.0
Endpoint	188	2.3	0.83	2.1	0.0, 4.0

SD=standard deviation; min=minimum; max=maximum. NOTE: Mean scores are first calculated for each patient from assessment performed within the treatment time period, then averaged across all patients. All visits with at least 10 patients are summarised. Global medication performance assessment was based on the scale 0=Poor, 1=Fair, 2=Good, 3=Very good, 4=Excellent.

6.1.3.3.2.2. Patient study medication questionnaire

The patient assessment of study medication questionnaire was added as an efficacy assessment after 53 patients had enrolled in the study. It was administered prior to the start of the long-term maintenance treatment period at visit -1/1, when new patients had completed titration and rollover patients had completed both titration and double-blind treatment for 10 episodes of BTP in the prior study, and at visit 2 (month 1).

Patient ratings of Oravescent fentanyl on the assessment of study medication questionnaire were favourable in all attributes rated: speed of onset of pain relief, ease of administration, and convenience of use, and patients generally preferred Oravescent fentanyl to their previous rescue medication.

Table 17: Study 099-15: Patient Study Medication Questionnaire Assessment (safety analysis set)

Question Response, n (%)	Number (%) of patients		
	Visit –1 New patients	Visit 1 Rollover patients	Visit 2 All patients
Which medication would you prefer to use when treating your breakthrough pain?	62 (100)	52 (100)	81 (100)
Study medication	59 (95)	44 (85)	71 (88)
Medication used for BTP prior to entering study	3 (5)	8 (15)	10 (12)
Which medication had a faster onset of pain relief?	60 (100)	50 (100)	81 (100)
Study medication	53 (88)	42 (84)	77 (95)

Question Response, n (%)	Number (%) of patients		
	Visit –1 New patients	Visit 1 Rollover patients	Visit 2 All patients
Medication used for BTP prior to entering study	7 (12)	8 (16)	4 (5)
Which medication was easier to administer?	61 (100)	52 (100)	82 (100)
Study medication	33 (54)	33 (63)	54 (66)
Medication used for BTP prior to entering study	28 (46)	19 (37)	28 (34)
Which medication was more convenient to use?	62 (100)	50 (100)	82 (100)
Study medication	35 (56)	32 (64)	56 (68)
Medication used for BTP prior to entering study	27 (44)	18 (36)	26 (32)
How do you rate the study medication in terms of onset of action?	62 (100)	52 (100)	82 (100)
Excellent	20 (32)	26 (50)	37 (45)
Good	34 (55)	22 (42)	39 (48)
Fair	8 (13)	4 (8)	6 (7)
Poor	0	1 (2)	0
How do you rate the study medication in terms of ease of administration?	62 (100)	52 (100)	82 (100)
Excellent	14 (23)	18 (35)	32 (39)
Good	38 (61)	25 (48)	34 (41)
Fair	9 (15)	8 (15)	14 (17)
Poor	1 (2)	1 (2)	2 (2)
How do you rate the study medication in terms of convenience of use?	62 (100)	52 (100)	82 (100)
Excellent	15 (24)	19 (37)	36 (44)
Good	34 (55)	26 (50)	31 (38)

Question Response, n (%)	Number (%) of patients		
	Visit –1 New patients	Visit 1 Rollover patients	Visit 2 All patients
Fair	11 (18)	6 (12)	13 (16)
Poor	2 (3)	1 (2)	2 (2)

NOTE: The patient assessment of study medication questionnaire was added to the study with protocol amendment 1. This summary includes responses only for patients who were at the summarised visits after protocol amendment 1. Visit -1 is summarised for new patients. Visit 1 is summarised for rollover patients.

6.1.3.3.2.3. Dose adjustments during study

Although dose adjustment was permitted at the discretion of the investigator during the long-term maintenance treatment period the doses remained relatively stable. Of the 197 patients in the maintenance safety analysis set, 69% had the same final dose at their final visit as their original successful dose. Dose changes were most frequent in the first month of the study and generally decreased in frequency over time. Development of incremental tolerance was the most frequent reason for dose changes at month 1 but seldom occurred at later visits.

6.2. Analyses performed across trials (pooled analyses and meta-analyses)

No meta-analyses or pooled analyses have been conducted. In Module 2.5 and 2.73 the sponsor did provide a summary of the two pivotal studies to demonstrate consistency of the results.

Table 18: Pivotal studies: Results of analyses of common efficacy variables

	Study 099-14 N=123		Study 3039 N=125	
Efficacy variable	Treatment difference[a]	Significance	Treatment difference[a]	Significance
Mean PID_{15}	0.3	p=0.0029	0.7	p<0.0001
Mean PID_{30}	0.9	p<0.0001	1.1	p<0.0001
Mean PID_{45}	1.4	p<0.0001	1.5	p<0.0001
Mean PID_{60}	1.7	p<0.0001	1.8	p<0.0001
Mean PR_{15}	0.3	p=0.0005	0.4	p<0.0001
Mean PR_{30}	0.5	p<0.0001	0.6	p<0.0001
Mean PR_{45}	0.8	p<0.0001	0.8	p<0.0001
Mean PR_{60}	0.8	p<0.0001	1.0	p<0.0001
$SPID_{30}$ (primary for Study 099-14)	1.2	p<0.0001	1.5	p<0.0001

	Study 099-14 N=123		Study 3039 N=125	
$SPID_{45}$	2.6	p<0.0001	3.0	p<0.0001
$SPID_{60}$ (primary for Study 3039)	4.3	p<0.0001	4.8	p<0.0001
$TOTPAR_{15}$	0.3	p=0.0001	0.2	p<0.0001
$TOTPAR_{30}$	0.6	p<0.0001	0.8	p<0.0001
$TOTPAR_{45}$	1.4	p<0.0001	1.7	p<0.0001
$TOTPAR_{60}$	2.2	p<0.0001	2.6	p<0.0001
Episodes with at least 33% improvement in PI_{30}	FEBT 49% Placebo 29%	Not calculated	FEBT 51% Placebo 26%	p<0.0001
Episodes with at least 33% improvement in PI_{60}	FEBT 76% Placebo 48%	Not calculated	FEBT 69% Placebo 33%	p<0.0001
Episodes with at least 50% improvement in PI_{30}	FEBT 25% Placebo 16%	Not calculated	FEBT 38% Placebo 15%	p<0.0001
Episodes with at least 50% improvement in PI_{60}	FEBT 65% Placebo 36%	Not calculated	FEBT 59% Placebo 22%	p<0.0001
Use of rescue medication	Odds ratio 3.25	95% CI 2.23, 4.72	Odds ratio 3.58	95% CI 2.23, 5.75

PID=pain intensity difference; PR=pain relief; SPID=summed pain intensity difference; TOTPAR=total pain relief; FEBT=fentanyl effervescent buccal tablet; CI=confidence interval. [a] Difference between means (not least squares means).

Figure 11: Pivotal Studies: Responder analysis of at least 50% improvement in pain intensity (FEBT vs placebo)

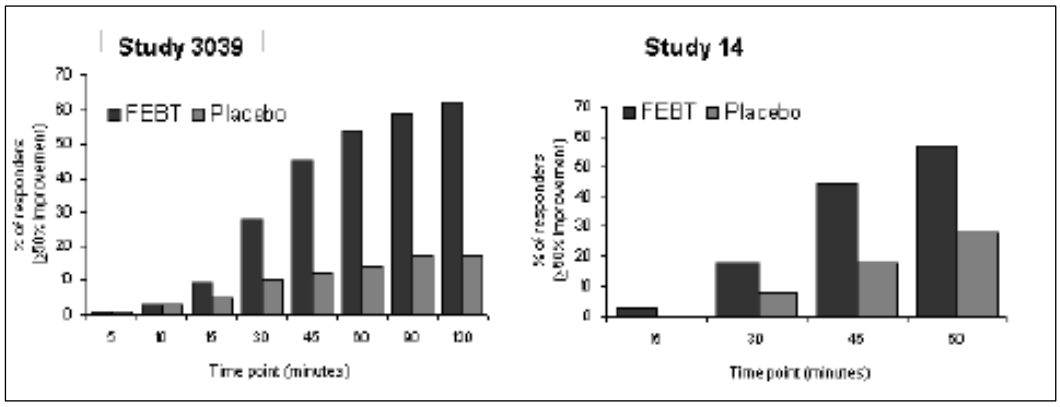
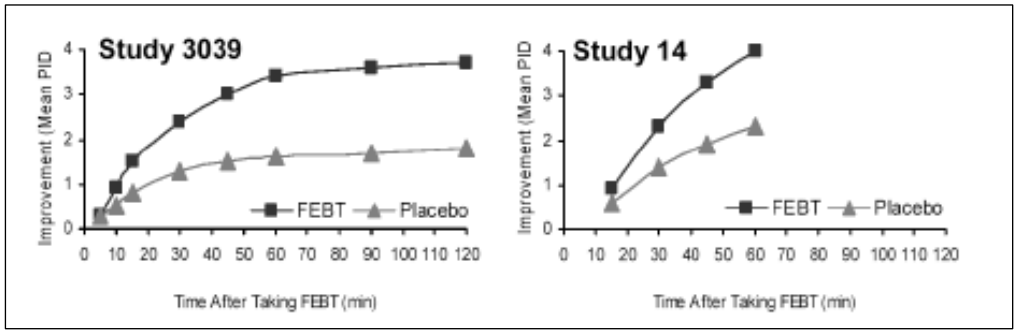


Figure 12: Pivotal studies: Time to analgesic effect (FEBT vs placebo)



6.3. Evaluator's conclusions on clinical efficacy for treatment of breakthrough pain in cancer patients

The efficacy is based on two pivotal studies (placebo controlled) and two open label studies. The two pivotal studies were of moderate size but similar design. The inclusion criteria were similar with the patients enrolled being typical of opioid tolerant adult men and women with cancer related background pain and breakthrough pain (BTP). They all were using around the clock (ATC) opioid therapy for their background pain and additional opioid therapy as rescue medication for their BTP. Both trials used a within patient control design which is necessary to minimise the risk of patients being treated with placebo.

The efficacy results from both pivotal studies showed a consistent positive effect for FEBT compared to placebo across the standard measures of pain (pain intensity, pain relief and use of rescue medication) and time points (15, 30, 45, and 60 minutes). At both the 30 and 60 minute time points a patient was twice as likely to achieve at least a 33% or 50% decrease in pain intensity with FEBT compared to placebo.

No active comparator trials have been conducted which is disappointing as a comparison to oral transmucosal fentanyl would have been useful to clinicians but the final decision will probably rest with patient preference.

All studies included a dose titration period and the comparison between starting doses of 100 µg and 200 µg indicated that a starting dose of the lower dose (100 µg) was the most appropriate. If patients could not determine an effective dose they did not continue in the studies.

The non-pivotal studies, which were open label non comparative studies provided some long term data demonstrating that the efficacy is maintained for up to 12 months.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal studies that assessed safety as a primary outcome

Not applicable

7.1.2. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study 4027 provided data on AEs, vital signs and oral mucosal examinations
- Study 099-15 provided data on AEs, laboratory tests, vital signs and oral mucosal examinations

7.1.3. Other studies evaluable for safety only

The submission included study reports for 5 studies in patients with non-cancer pain and BTP and 2 studies with mixed populations of patients with BTP. The studies have not been individually evaluated but they were included in the Summary of Clinical Safety and reference is made where this relevant.

7.1.4. Clinical pharmacology studies

The safety results for the clinical pharmacology studies are provided in summaries.

7.2. Patient exposure

The primary safety analysis set is made up of the following studies:

- Pivotal double blind, placebo controlled studies - Studies 099-14 and 3039
- Open label study – Study 099-15

An additional study (4027) was included in the submission. It is included in the Summary of Clinical Safety but the data for this trial was not integrated with the other data. It is presented separately as “supportive safety data”.

Data from the studies in non-cancer pain is only referenced where relevant.

Table19: Exposure to FEBT and comparators in clinical studies.

Study type/ Indication	FEBT			Total FEBT
Clinical pharmacology Single dose Multiple dose	 596 35			 596 35
	Controlled studies		Uncontrolled studies	
Indication BTP	FEBT	Placebo	FEBT	
Pivotal				

Study type/ Indication	FEBT			Total FEBT
099-14				
titration	123	123		123
post titration	77	77		77
3039				
titration	125	125		125
post titration	86	86		86
Other				
099-15				
titration			115	115
post titration			197	197
4027				
titration			312	312
post titration			223	223
TOTAL				
titration	248	248	670	1306
post titration	163	163	462	1214

Table 20: Exposure to FEBT in clinical Studies 099-14, 3039 and 099-15 according to dose

Variable Category	Number (%) of patients (N=358)
Successful dose (µg)	
None	113 (32)
100	23 (6)
200	33 (9)
400	54 (15)
600	59 (16)

Variable Category	Number (%) of patients (N=358)
800	76 (21)
Maximum dose (µg)	
100	38 (11)
200	33 (9)
400	62 (17)
600	57 (16)
800	168 (47)
Average dose per BTP episode (µg)[a]	
<200	49 (14)
≥200-<400	91 (25)
≥400-<600	100 (28)
≥600-<800	79 (22)
≥800	18 (5)
Missing	21 (6)
Average daily dose (µg)[a]	206 (58)
≤800 µg	
>800-≤1600 µg	54 (15)
>1600-≤2400 µg	27 (8)
>2400-≤3200 µg	47 (13)
>3200 µg	21 (6)
Missing	3 (<1)

a The average dose per BTP episode and the average daily dose were calculated for the titration and post titration periods combined. BTP=breakthrough pain.

Table 21: Average Study Drug Dose per Breakthrough Pain Episode by Weeks or Months of Exposure in Patients with Cancer and Breakthrough Pain. Studies 099-14, 3039, 099-15.

Length of exposure	Number (%) of patients by average dose per BTP episode (mcg)						
	<200 (N=49)	≥200-<400 (N=91)	≥400-<600 (N=100)	≥600-<800 (N=79)	≥800 (N=18)	Missing [a] (N=21)	Total (N=358)
≥1 day	49 (100)	91 (100)	100 (100)	79 (100)	18 (100)	21 (100)	358 (100)
≥1 week	27 (55)	69 (76)	75 (75)	79 (100)	17 (94)	4 (19)	271 (76)
≥2 weeks	19 (39)	54 (59)	63 (63)	74 (94)	16 (89)	2 (10)	228 (64)
≥1 month	17 (35)	35 (38)	53 (53)	67 (85)	16 (89)	1 (5)	189 (53)
≥3 months	7 (14)	24 (26)	38 (38)	53 (67)	12 (67)	0	134 (37)
≥6 months	3 (6)	15 (16)	18 (18)	33 (42)	11 (61)	0	80 (22)
≥9 months	2 (4)	12 (13)	12 (12)	20 (25)	8 (44)	0	54 (15)
≥12 months	2 (4)	10 (11)	8 (8)	14 (18)	5 (28)	0	39 (11)
≥15 months	1 (2)	6 (7)	4 (4)	8 (10)	2 (11)	0	21 (6)
≥18 months	1 (2)	1 (1)	3 (3)	4 (5)	1 (6)	0	10 (3)

a Average dose per day cannot be calculated due to incomplete diary data. BTP=breakthrough pain.

Table 22: Extent of exposure to the study drug in Study 4027

Variable	Titration period			Treatment period	Continuation period	All periods
	100 µg (N=145)	200 µg (N=167)	Total (N=312)	Overall (N=223)	Overall (N=87)	Overall (N=223)
Duration of treatment (days)						
N	144	162	306	219	87	223
Mean	5.5	5.5	5.5	4.8	204.2	90.6
SD	2.02	1.97	1.99	1.89	198.66	158.26
SE of mean	0.17	0.15	0.11	0.13	21.30	10.60
Median	6.5	6.0	6.0	4.0	115.0	14.0
Min, max	1, 10	1, 12	1, 12	1, 12	1, 684	1, 688
Total dose (mcg)						
n	144	167	311	222	—	—
Mean	2995.8	3620.4	3331.2	2552.7	—	—
SD	3207.77	3107.75	3164.75	1918.65	—	—
SE of mean	267.31	240.49	179.46	128.77	—	—
Median	1950.0	2700.0	2400.0	1600.0	—	—
Min, max	100, 20800	200, 17000	100, 20800	0, 12000	—	—
Average dose per episode (µg)						
n	144	167	311	222	—	—
Mean	250.1	330.3	293.1	309.5	—	—
SD	152.70	157.04	159.90	196.00	—	—
SE of mean	12.73	12.15	9.07	13.15	—	—
Median	200.0	300.0	230.8	200.0	—	—
Min, max	100, 743	100, 757	100, 757	0, 800	—	—

NOTES: The titration safety analysis set is presented by randomized treatment group. The average dose per episode is the total dose divided by the number of episodes in the titration/treatment period. Max=maximum; min=minimum; n=number of patients with a response; SD=standard deviation; SE=standard error.

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

Comment: In neither the study reports or Summaries is there a comparison of the AEs on study drug compared to placebo.

7.3.1.1. Studies 099-14, 3039, 099-15

A total of 206 (58%) patients with cancer and BTP had at least 1 AE during the titration period and 217 (91%) had at least 1 AE during the post titration period. The most frequently occurring AEs in the post titration period were nausea, vomiting, fatigue, constipation, anaemia, peripheral oedema, headache, dizziness, asthenia and dehydration, depression, anorexia and abdominal pain.

Table 23: Adverse Events Occurring in ≥5% of Patients with Cancer and Breakthrough Pain Overall by Average Daily Dose (Studies 099-14, 3039, 099-15)

MedDRA system organ class Preferred term	Number (%) of patients[a]						
	≤800 µg (N=206)	>800-≤1600 µg (N=54)	>1600-≤2400 µg (N=27)	>2400-≤3200 µg (N=47)	>3200 µg (N=21)	Missing (N=3)	Total (N=358)
Patients with at least 1 adverse event	166 (81)	49 (91)	26 (96)	42 (89)	21 (100)	1 (33)	305 (85)
Blood and lymphatic system disorders							
Anaemia	18 (9)	8 (15)	3 (11)	8 (17)	3 (14)	0	40 (11)
Neutropenia	6 (3)	4 (7)	1 (4)	6 (13)	1 (5)	0	18 (5)
Gastrointestinal disorders							
Nausea	54 (26)	15 (28)	13 (48)	19 (40)	9 (43)	0	110 (31)
Vomiting	30 (15)	9 (17)	6 (22)	13 (28)	5 (24)	0	63 (18)
Constipation	25 (12)	8 (15)	4 (15)	9 (19)	2 (10)	0	48 (13)
Diarrhoea	11 (5)	7 (13)	4 (15)	4 (9)	3 (14)	0	29 (8)

MedDRA system organ class Preferred term	Number (%) of patients[a]						
	≤800 µg (N=206)	>800-≤1600 µg (N=54)	>1600-≤2400 µg (N=27)	>2400-≤3200 µg (N=47)	>3200 µg (N=21)	Missing (N=3)	Total (N=358)
Abdominal pain	3 (1)	9 (17)	4 (15)	9 (19)	2 (10)	0	27 (8)
Stomatitis	11 (5)	4 (7)	1 (4)	4 (9)	0	0	20 (6)
General disorders and administration site conditions							
Fatigue	25 (12)	11 (20)	8 (30)	10 (21)	4 (19)	0	58 (16)
Oedema peripheral	18 (9)	7 (13)	2 (7)	5 (11)	6 (29)	0	38 (11)
Asthenia	15 (7)	8 (15)	1 (4)	7 (15)	3 (14)	0	34 (9)
Pyrexia	8 (4)	7 (13)	4 (15)	4 (9)	0	0	23 (6)
Infections and infestations							
Pneumonia	12 (6)	3 (6)	2 (7)	5 (11)	2 (10)	0	24 (7)
Urinary tract infection	6 (3)	3 (6)	3 (11)	6 (13)	0	0	18 (5)
Investigations							
Weight decreased	10 (5)	6 (11)	1 (4)	4 (9)	1 (5)	0	22 (6)
Metabolism and nutrition disorders							
Dehydration	20 (10)	5 (9)	1 (4)	6 (13)	1 (5)	0	33 (9)
Anorexia	7 (3)	3 (6)	4 (15)	9 (19)	2 (10)	0	25 (7)
Hypokalaemia	7 (3)	2 (4)	2 (7)	5 (11)	2 (10)	0	18 (5)

MedDRA system organ class Preferred term	Number (%) of patients[a]						
	≤800 µg (N=206)	>800-≤1600 µg (N=54)	>1600-≤2400 µg (N=27)	>2400-≤3200 µg (N=47)	>3200 µg (N=21)	Missing (N=3)	Total (N=358)
Musculoskeletal and connective tissue disorders							
Arthralgia	4 (2)	10 (19)	4 (15)	3 (6)	1 (5)	0	22 (6)
Back pain	8 (4)	3 (6)	4 (15)	4 (9)	1 (5)	0	20 (6)
Nervous system disorders							
Dizziness	45 (22)	14 (26)	6 (22)	13 (28)	5 (24)	0	83 (23)
Headache	25 (12)	8 (15)	5 (19)	10 (21)	4 (19)	0	52 (15)
Somnolence	17 (8)	10 (19)	6 (22)	6 (13)	2 (10)	0	41 (11)
Psychiatric disorders							
Depression	12 (6)	7 (13)	2 (7)	4 (9)	0	0	25 (7)
Anxiety	10 (5)	1 (2)	4 (15)	3 (6)	2 (10)	0	20 (6)
Confusional state	10 (5)	2 (4)	1 (4)	4 (9)	1 (5)	0	18 (5)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	10 (5)	4 (7)	1 (4)	7 (15)	1 (5)	0	23 (6)
Cough	10 (5)	2 (4)	1 (4)	4 (9)	2 (10)	0	19 (5)

a Patients may have had more than 1 adverse event type, but are counted only once in each preferred term category and in each high-level category. MedDRA=Medical Dictionary for Regulatory Activities. NOTE: Includes studies 14, 3039, and 15. Data are combined for the titration and the post titration treatment periods. Data are included for adverse events in at least 5% of patients overall.

7.3.1.2. Study 4027

During the titration period, 118 (37.8%) of the 312 patients had at least 1 AE. For the 100 and 200 µg treatment groups combined, the most frequently occurring adverse events were nausea

(19 [6.1%] of patients), vomiting (15 [4.8%]), dizziness (12 [3.8%]), and somnolence (11 [3.5%]).

Table 24: Study 4027: AEs occurring in ≥2% patients in any treatment group or overall

System organ class MedDRA preferred term	Number (%) of patients			
	Titration period			Treatment period
	100 µg group (N=145)	200 µg group (N=167)	Total (N=312)	Overall (N=223)
Patients with at least 1 adverse event	44 (30.3)	74 (44.3)	118 (37.8)	43 (19.3)
Gastrointestinal disorders				
Constipation	3 (2.1)	2 (1.2)	5 (1.6)	3 (1.3)
Nausea	7 (4.8)	12 (7.2)	19 (6.1)	5 (2.2)
Vomiting	4 (2.8)	11 (6.6)	15 (4.8)	2 (0.9)
Nervous system disorders				
Dizziness	5 (3.4)	7 (4.2)	12 (3.8)	0
Somnolence	7 (4.8)	4 (2.4)	11 (3.5)	1 (0.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	3 (2.1)	1 (0.6)	4 (1.3)	1 (0.4)

MedDRA= Medical Dictionary for Regulatory Activities. NOTES: Adverse events occurring before administration of study drug were not included in this summary table. Adverse events were coded using MedDRA v13.0.

7.3.2. Treatment-related adverse events (adverse drug reactions)

Comment: No integrated summary is presented of the AEs considered related to study drug. The following is taken from the individual study reports. Pivotal studies

7.3.2.1. Study 099-14

40 (33%) patients experienced treatment-related adverse events during the dose titration period and 14 (18%) patients experienced treatment-related adverse events during the double-blind treatment period. The most frequently occurring treatment-related adverse events overall in the study were the following: dizziness (18%), nausea (10%), somnolence (8%), headache (7%), and fatigue (5%). Only dizziness (16% versus 6%) and headache (7% versus 1%) occurred at different rates in the dose titration period versus the double blind treatment period. No treatment-related adverse events appeared to be dose related.

7.3.2.2. Study 3039

Of the 83 patients who had any adverse event, over half (42 patients) had 1 or more adverse events considered treatment related (possibly, probably, or definitely related). Treatment-related adverse events were experienced by 33 (26%) patients during the dose titration period, 14 (16%) patients during the double-blind treatment period, and 42 (34%) patients overall, ie, during both periods of the study. Of the most frequently occurring (in at least 5% of patients) adverse events that occurred during the study, dizziness and nausea were most frequently considered treatment related.

7.3.2.3. Other studies

7.3.2.3.1. Study 099-15

Overall, 108 (47%) patients experienced treatment-related (possibly, probably, or definitely related, or missing relationship) adverse events during the study; 51 (46%) patients experienced treatment-related adverse events during the dose titration period and 75 (38%) patients experienced treatment-related adverse events during the long-term maintenance treatment period. The most frequently (in at least 10% of patients) occurring treatment-related adverse events overall in the study were nausea and dizziness (16% each). Other treatment-related adverse events occurring in at least 5% of patients were somnolence (9%), constipation (7%), and headache (5%).

7.3.2.3.2. Study 4027

Of the 201 patients in the analysis set with at least 1 adverse event during the titration, treatment, and continuation periods, 75 (24.0%) patients had adverse events that were considered to be treatment-related. For the most frequently occurring adverse event of nausea half of the occurrences were considered to be related to study drug administration. For the other most frequently occurring adverse events in patients receiving fentanyl based maintenance therapy, less than half of the occurrences of vomiting (in 6 of 13 patients) were considered to be related to study drug administration, and none of the occurrences of malignant neoplasm progression or back pain was considered to be related to study drug administration.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Studies 099-14, 3039 and 099-15

7.3.3.1.1. Deaths

Of a total of 73 deaths reported, 69 occurred after patients had stopped taking study drug (more than 1 day) prior to death. No patients died during the titration period of the study. 4 patients died during the maintenance period all due to their cancer. No death was considered to be related to study drug.

7.3.3.1.2. Other SAEs

A total of 131 (37%) patients experienced at least 1 SAE. Of these, 73 subsequently died. The most frequently reported SAEs were pneumonia (17 [5%] patients), dehydration (12 [3%] patients), vomiting and respiratory failure (7 [2%] patients each), and cancer pain, nausea and confusional state (each in 6 [2%] patients). Most of the SAEs appeared to be related to the patient's underlying condition. Only 1 SAE (drug withdrawal syndrome) was considered to be treatment related.

7.3.3.2. Study 4027

7.3.3.2.1. Deaths

A total of 52 patients in the randomised set died during the study (including 10 patients who had not received study drug). The most frequently occurring adverse events with a fatal outcome were lung neoplasm malignant and malignant neoplasm progression (both 2 patients;

0.6%) in the titration period, respiratory failure (2 patients; 0.9%) in the treatment period (both considered to be related to the underlying disease), and malignant neoplasm progression (15 patients; 17.2%) in the continuation period.

7.3.3.2.2. Other SAEs

A total of 71 patients in the randomised set had 1 or more SAEs during the study (20 during the titration period, 4 during the treatment period and37 during the continuation period). The most frequently occurring SAEs were lung neoplasm malignant, malignant neoplasm progression, and renal failure (all in 2 patients; 0.6%) in the titration period, respiratory failure (2 patients; 0.9%) in the treatment period (both considered to be related to the underlying disease), and malignant neoplasm progression (15 patients; 17.2%) in the continuation period. The majority of serious adverse events were considered to be related to the underlying disease by the investigator.

7.3.3.3. Studies in non-cancer patients

7.3.3.3.1. Deaths

There were 6 deaths in the cohort of 1490 patients in the 5 studies of patients with non-cancer pain and BTP and in 2 studies of chronic pain and BTP. 5 deaths were due to cardiac related events and 1 from pneumonia. All 6 cases were considered to be unrelated to study drug.

7.3.3.3.2. Other SAEs

The total number of SAEs in the 7 non-cancer trials was low (~12%). All SAEs occurred in less than 1% of patients. The most frequently occurring SAEs were pneumonia, myocardial infarction, vomiting, nausea, abdominal pain, chest pain, drug withdrawal syndrome, cholelithiasis, cellulitis, gastroenteritis, back pain and syncope.

7.3.4. Discontinuation due to adverse events

7.3.4.1. Studies 099-14, 3039 and 099-15

A total of 111 (31%) patients withdrew from the studies due to 1 or more adverse events. The most frequently reported AEs leading to discontinuation from the studies were nausea, vomiting, and dizziness. AEs related to the application site led to the discontinuation of 7 (2%) patients. Most discontinuations due to AEs were considered not related or unlikely related to treatment with study drug. Approximately half (55 of 111) the patients who withdrew from the study did so because of AEs in the system organ class neoplasms benign, malignant and unspecified.

7.3.4.2. Study 4027

A total of 55 patients had an AE leading to discontinuation from the study. The most frequently occurring AEs leading to discontinuation were nausea and vomiting in the titration period and malignant neoplasm progression in the continuation period.

7.3.5. Adverse events of special interest

AEs of special interest were not summarised for Study 4027 and so the following relates only to Studies 099-14, 4027 and 099-15. The total patient dataset is 363.

7.3.5.1. AEs associated with opioid use

The overall frequency of adverse events associated with opioid use was as follows: nausea (31%), dizziness (23%), vomiting (18%), constipation (13%), somnolence (11%), anxiety (6%), and tremor (4%). The frequency was expected in patients with cancer and BTP. Sedation occurred in 5 (1%) patients. For most adverse events associated with opioid use, there was no apparent dose-related pattern. Most of the AEs occurred only once and were of short duration and mostly mild or moderate in severity.

7.3.5.2. AEs associated with drug withdrawal syndrome

Two (2) patients had an AE of drug withdrawal syndrome. One was associated with oxycodone and gabapentin withdrawal symptoms of moderate severity considered by the investigator to not be study drug related. The second case was a SAE of drug withdrawal syndrome considered by the investigator to be related to study drug. The patient had been taking up to 11 800 µg FEBT tablets daily and suddenly stopped.

AEs of anxiety and tremor were the only AEs commonly associated with drug withdrawal occurring in at least 1% of patients. 20 patients reported anxiety, of which 17 reported only 1 episode. The maximum duration was 1 week or less in 19/20 patients. Tremor was reported by 15 patients, 13 or which had only one episode. The maximum duration was 1 week or less in 14/15 patients.

7.3.5.3. AEs of respiratory depression or failure

There were no reports of respiratory depression in the studies. 7 patients reported respiratory failure and 1 patient reported acute respiratory failure. None of these patients reported sedation, somnolence or confusion that were temporally associated with the respiratory failure. In each case the event was considered by the investigator to be related to the patient's underlying condition and not related to the study drug.

7.3.5.4. AEs of pneumonia

A total of 17 patients had SAEs of pneumonia. 13 of these patients had no associated AE of nausea or vomiting near the time of the pneumonia. One patient had a SAE of aspiration pneumonia said to be recurrent as the patient had a history of recurrent aspiration at study entry and the event was considered to be related to the patient's underlying condition and not related to study drug.

7.3.5.5. AEs associated with the application site

31 (9%) of patients had AEs considered related to the application site – 20 patients had events that were symptomatic and 17 had physical findings related to the application site. 7 patients with application site abnormalities withdrew from the studies, 4 during the titration period and 3 during the post titration period. The AEs resolved with no residual effect in 88% of cases and were continuing in 12% at study end.

Table 25: Adverse Events Related to the Application Site by Preferred Term in Patients with Cancer and Breakthrough Pain

MedDRA system order class	Number (%) of patients
Higher-level term	(N=358)
Preferred term	
Patients with application site adverse events[a]	31 (9)
General disorders and administration site conditions	31 (9)
Application and instillation site reactions	31 (9)
Application site pain	12 (3)
Application site ulcer	11 (3)

MedDRA system order class	Number (%) of patients
Application site irritation	8 (2)
Application site paraesthesia	4 (1)
Application site reaction	3 (<1)
Application site anaesthesia	2 (<1)
Application site erythema	2 (<1)
Application site oedema	1 (<1)
Application site swelling	1 (<1)
Application site vesicles	1 (<1)

a Includes patients with physical findings related to the application site. MedDRA=Medical Dictionary for Regulatory Activities. NOTE: Order of preferred terms was determined by frequency of occurrence in all patients.

Oral mucosal examinations were performed at each visit in each study. A newly diagnosed oral mucosal examination finding was defined as being normal or missing at baseline and abnormal at least once during the study. A total of 29 (8%) patients with cancer and BTP had at least 1 newly diagnosed oral mucosal examination finding.

7.4. Laboratory tests

7.4.1. Clinical chemistry and haematology

Overall, mean changes in most chemistry variables observed in the efficacy studies were not considered clinically meaningful. There was no evidence of any trends in mean changes from baseline to endpoint for any clinical chemistry or haematology parameter in patients treated with FEBT. The abnormalities that were seen were not unexpected in patients with cancer and were consistent with the patient's medical history and abnormal laboratory values at baseline or explained by concomitant medications or by adverse events occurring during the study that were considered unrelated to study drug.

In the studies in non-cancer pain with BTP there were also no trends in mean changes from baseline to endpoint for any serum chemistry or haematology variables with treatment with FEBT.

7.4.2. Vital signs

All changes in vital signs were small and not considered clinically meaningful. Vital signs were monitored for an hour after the first administration of the study drug (FEBT test dose of 100 µg in Studies 09914 and 099-15) and no meaningful changes were observed during the period of peak fentanyl concentration. A number of patients had clinically significant abnormal vital sign measurements but were consistent with the known association of opioid analgesics with hypotension.

Again a similar profile was seen in the non-cancer patients treated with FEBT.

7.5. Post-marketing experience

FEBT was first registered in the USA in September 2006 and marketed from October 2006. As of September 2011 it was approved in 31 countries and marketed in 10 (USA, Austria, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain and the United Kingdom). Cumulatively through 31 March 2011, worldwide post marketing usage of FEBT is estimated at 18, 538 patient treatment years.

13 PSURs were included in the submission covering the period September 2006 to April 2012.

Spontaneous reports received have been consistent with the safety profile observed in the clinical trials. The following new AEs have been identified during the post marketing period: loss of consciousness, respiratory arrest, and drug tolerance.

The sponsor also submitted a Prescription Event Monitoring Report from the Drug Safety Research Trust, which operates in association with the University of Portsmouth. This drug utilisation study was conducted from March 2009 to June 2011 and included 551 evaluable patients who had been prescribed FEBT as part of normal practice by GPs in England. Overall the prescribing was found to be in line with the approved SmPC. The median time from test dose to effective dose was 19.5 days. Where specified (n=201), the most frequent effective dose reported was 100 µg (n=66), as was the dose reported on initiation of maintenance regimen of fentanyl buccal tablets (n=72 of 200 responses). There were four reports of doses in excess of 800 µg for both the effective and maintenance dose; one report of 1,000 µg, two reports of 1,200 µg and one of 3,200 µg. There were no new safety events identified. There were no cases of respiratory failure reported during treatment nor obliterative bronchiolitis, however there was one case of respiratory depression reported. There were two cases of opioid withdrawal syndrome reported during treatment with fentanyl buccal tablets and four cases of overdose reported.

7.6. Safety issues with the potential for major regulatory impact

7.6.1. Overdose

There was one report of overdose in the studies in patients with cancer and BTP (in Study 4027). The overdose occurred during the titration phase of the study and it is unknown if the overdose was accidental or intentional. The patient was recorded as non-compliant with the study drug due to taking study drug more frequently than every 4 hours for 3 days. The patient was discontinued from the study because of the overdose and because of progression of cancer.

In the non-cancer studies there were 12 cases of overdose reported. No event was fatal. Three events were intentional, occurring in the context of suicide attempts and in another the study drug was used in combination with alcohol. In three other cases the patients had medical factors (pneumonia, head trauma and drug interaction) that were considered to have contributed to the overdose. Four patients had overdoses that were considered accidental and for 1 patient the exact circumstances were not known. A final case related to the overdose death of the [information redacted] of a study participant. The patient reported that [information redacted] had taken [information redacted] study drug (800 µg) as 12 to 18 tablets were missing and autopsy reported that the patient's [information redacted] died from fentanyl overdose.

7.6.2. Dependence, rebound phenomena, abuse, tolerance

Physical dependence is a known characteristic with fentanyl treatment, as with other opioids. The potential for developing dependence is difficult to assess in an opioid tolerant patient population. In the clinical programme FEBT was used on an as needed basis by patients with an average of 1-4 BTP episodes per day and who were already taking ATC opioids. The short term studies allowed only 1 tablet per episode, and in the long term study a maximum of 2 tablets was permitted per BTP episode. Consequently no specific evaluations have been made of the potential for withdrawal and/or rebound effects with FEBT.

Fentanyl has a significant well documented abuse potential. FEBT may be attractive for abuse because of the rapid rise of fentanyl blood levels although the peak plasma concentration and the time to reach the peak are notably lower than after intravenous administration. Although the risk of extraction of fentanyl from the tablets is present, manipulation (eg crushing) of the tablet is not likely to substantially alter the absorption characteristics of the medication when administered buccally or orally. Although intranasal and intravenous administration of a crushed tablet is possible, the risk of such is not considered to be any greater for FEBT than for any other strong μ-opioid drugs such as oxycodone, hydromorphone or morphine.

7.7. Other safety issues

7.7.1. Safety in special populations

7.7.1.1. Age

Patients over the age of 65 years tended to require lower doses of FEBT but the overall incidence of AEs was comparable in younger (≤65 years) and older (>65 years) patients (86% and 83% respectively). Among the common AEs, AEs reported with a marked difference by age groups (at least 5% described by preferred terms) is shown in the table below.

Table 26: Adverse events by age groups (Studies 099-14, 3039 and 099-15)

Adverse event	≤65 years N=282 N (%)	>65 years N=76 N (%)
Higher in older		
Constipation	35 (12)	13 (17)
Upper abdominal pain	5 (2)	5 (7)
Dysphagia	5 (2)	5 (7)
Cancer pain	8 (3)	7 (9)
Lethargy	7 (2)	5 (7)
Higher in younger		
Fatigue	49 (17)	9 (12)
Neutropenia	17 (6)	1 (1)
Oedema peripheral	33 (12)	5 (7)
Headache	45 (16)	7 (9)

7.8. Safety related to drug-drug interactions and other interactions

No clinical drug-drug interactions were performed. Fentanyl is known to be primarily metabolised in the liver and intestinal mucosa by the cytochrome P450 (CYP) CYP3A4/5 isoforms to norfentanyl. There is no expectation that FEBT would be any different to any other formulation of fentanyl in terms of metabolism or likely interactions. The Product Information contains the appropriate warnings about potential drug interactions.

7.9. Evaluator's overall conclusions on clinical safety

The total patient numbers in the safety assessment is low but fentanyl is a well know substance and the new dosage form and route of administration is not significantly different to other approved products. There is some concern of the paucity of long term data – nearly half the patients received the drug for less than 1 month but this may be representative of the patients likely to be prescribed the product.

No new safety issues emerged in the clinical studies. The most common AEs reported with FEBT treatment were characteristic of fentanyl products, namely nausea, dizziness, constipation, fatigue, headache and vomiting. The incidence and types of adverse events did not appear to be dose related. Further the rapid absorption of FEBT did not appear to affect the type or severity of the AEs reported.

Approximately 10% of patients experienced AEs that could be considered to be related to the tablet application site, eg application site pain, ulcer or burning. In the majority of patients these AEs were mild to moderate and resolved without treatment interruption. Women appeared to be at greater risk for application site events. Application site AEs could be reduced if the patient is advised to alternate the placement of the tablet in the right and left buccal mucosa or to administer the tablet sublingually.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Fentora in the proposed usage are:

- FEBT at a range of individually titrated doses (from 100-800 µg) was superior to placebo in relieving BTP in cancer patients on maintenance ATC opioid therapy as measured by a range of pain measures including pain intensity, pain relief, rescue medication used and global medication performance
- Most patients were able to achieve a successful dose with a simple titration schedule starting at 100 µg.

8.2. First round assessment of risks

The risks of Fentora in the proposed usage are:

- Known AEs to fentanyl – nausea and vomiting, dizziness, constipation, fatigue and headache
- Respiratory depression
- Dependency and abuse – but less likely in the indication being sought.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Fentora, given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

Based on the clinical data submitted in Module 5 it is recommended that Fentora be approved.

10. Clinical questions

No clinical questions were raised by the clinical evaluator.

11. Second round evaluation of clinical data submitted in response to questions

As no clinical questions were raised by the clinical evaluator, no second round evaluation was conducted.

12. References

1. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 1998; 90:611-6.

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