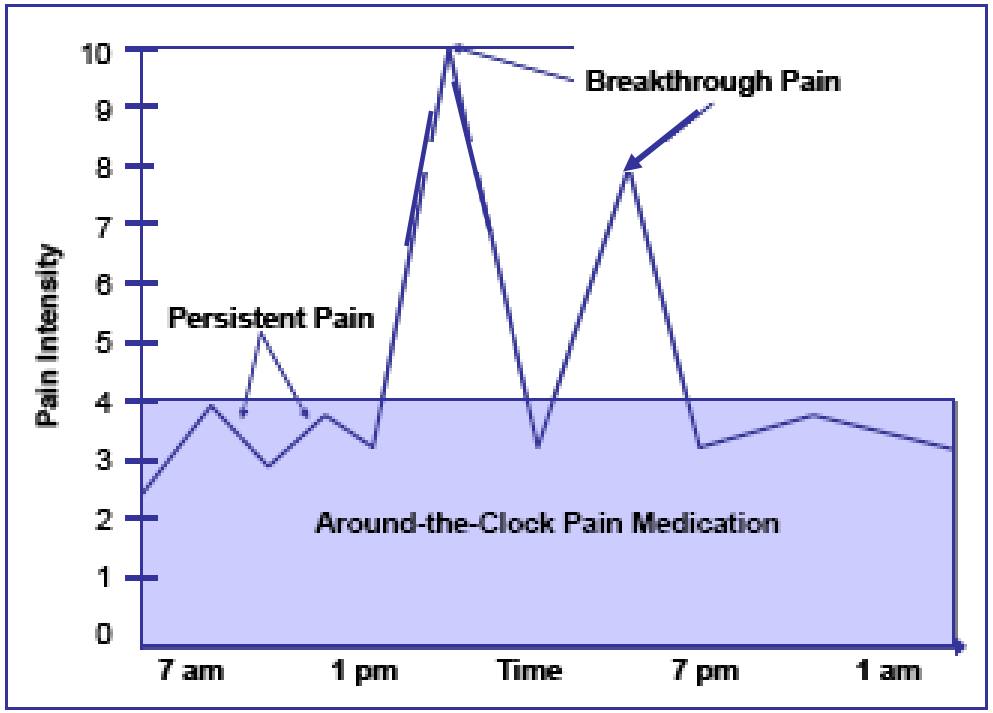
Pain Control

Figure 1. Breakthrough pain[35,36]



Persistent pain

+

Breakthrough pain

Adapted from Taylor, D.R., & Webster, L.R. (2005). The recognition and management of noncancer breakthrough pain. Retrieved Jul. 31, 2007, from http://www.medscape.com/viewarticle/516583_4

Breakthrough pain

Temporal pattern

- Median episodes – 4/day (range 1-60/day)
- Peak onset – 3 min *(43% of the 53 patients)* **to 5 min**
- Median duration – 30 min (range 1-240min)[1]

Intensity

- Slight - 16% *(n= 58)*
- Moderate - 46% *(n=167)*
- Severe - 36% *(n= 128)*
- Excruciating - 2% *(n= 8)* [2]

1-Portenoy, 1990
2- Zeppetella, 2000

Fentora™

(fentanyl buccal/Sublingual tablet)

Fentanyl properties

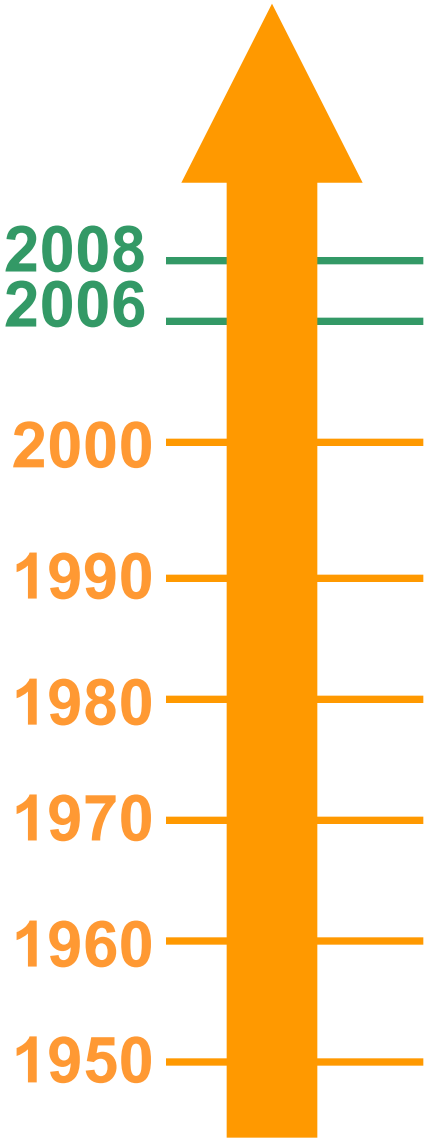
- Highly lipophilic: crosses membranes rapidly
- Rapid redistribution into tissue
- Protein binding 80-85%
- Extensive first-pass metabolism
- Hepatic metabolism primarily by CYP 3A4
- Metabolites not pharmacologically active
- Mainly renal excretion
- Crosses the placenta and has been detected in breast milk.

Martindale

Fentanyl

- Estimated potency 80 times that of morphine
- No ceiling effect for analgesia
- “Clean drug”

Fentanyl story



- **Fentora™ 4.04.08**
- **FENTORA™ 25.09.06**
- ACTIQ® fentanyl citrate lozenge (1998US-2000 EU)
- *Sufentanil* (1998)
- Duragesic® transdermal patch (1993)
- *Alfentanil* (1984)
- **1st medical use** in the 1960s as intravenous anaesthesic SUBLIMAZE®
- **1st synthesised** in Belgium in the **late1950s**

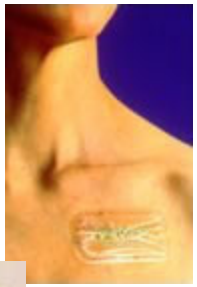
the Oromucosal route

- **"Convenient" routes:**

Oral (tablet, syrup), Sublingual

- Drug is swallowed and absorbed by the **gastrointestinal tract**
- Absorption may be incomplete due to **first-pass metabolism**
- Absorption may be **delayed** due to physiological factors

Transdermal



➔
- Avoids the first pass effect
- Does not provide a fast action

Rectal

➔
- Partially avoids first pass-effect
- Variability of absorption

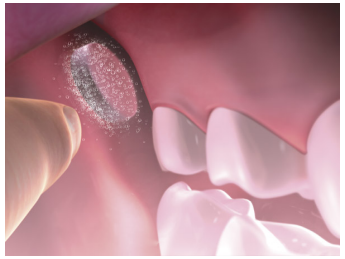
Nasal

➔
- Avoids first pass-effect
- Nasal irritation in some patients

Oromucosal

Oral Transmucosal Delivery

- **Oral transmucosal delivery**
  - Long history: nitroglycerine 1800s
  - Oral mucosa is composed of epithelial cells[1]
    - no keratin
  - Allows direct access to the systemic circulation



- **Convenient route**
- Drug is partially absorbed across buccal or **sublingual mucosa**
- May permit drug to reach point of action **sooner**
- Nevertheless, some drug (and in certain cases a substantial amount) may still be swallowed and undergo first-pass metabolism

1- Zhang, 2002, 663

Rational: the needs

- 50-90% of patients treated for chronic cancer pain experience BTCP episodes[1]
- SAOs are the current standard treatment for BTCP[2]
- ACTIQ® has a shorter onset of action[3] compared with orally administered fentanyl but it has some drawbacks with the mode of administration
- Still need to improve the time to onset of pain relief

BTCP = BreakThrough Cancer Pain; SAO= Short Acting Opiods

1-Portenoy, 1999; 2-S Mercadante American Cancer society 2002; 3-Zeppetella G, *The Cochrane Library* 2007, Issue 2

OraVescent® Technology (OVT): *A Novel Drug Delivery System*

Dynamic Alteration of Salivary pH

- For drugs characterised as weak bases *(eg fentanyl)*

↓ pH

Ionised molecules

↳ **↑ DISSOLUTION**

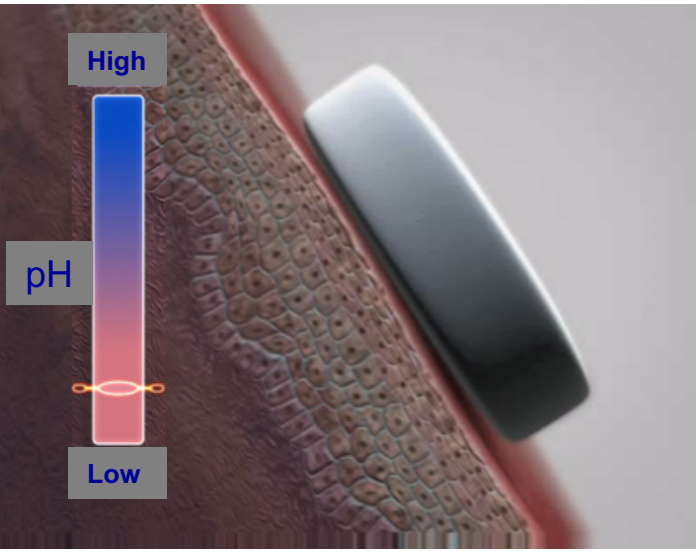
↑ pH

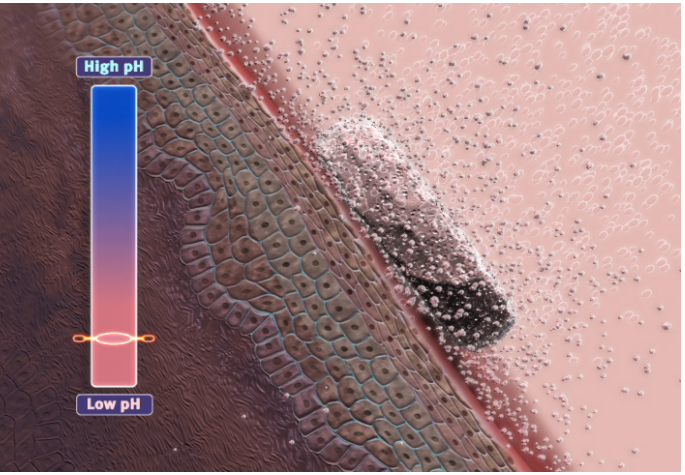
NON Ionised molecules

↳ **↑ ABSORPTION**

Note : Most oral transmucosal drug delivery methods have **little effect** on the **pH of saliva**, which is roughly neutral
Generally less than optimal

Optimising Dissolution





Pather et al (2001). *Drug Deliv Tech,* 1: 54-57.
Durfee et al (2006). *Am J Drug Deliv.* 4: 1-5.

Tablet + saliva = Acid + saliva

$C_6H_8O_7$ + $3HCO_3^-$ → $3H_2CO_3$ + $C_6H_5O_7^{3-}$

citric acid — bicarbonate — carbonic acid — citrate

↳ ↓ pH

↳ Ionic form

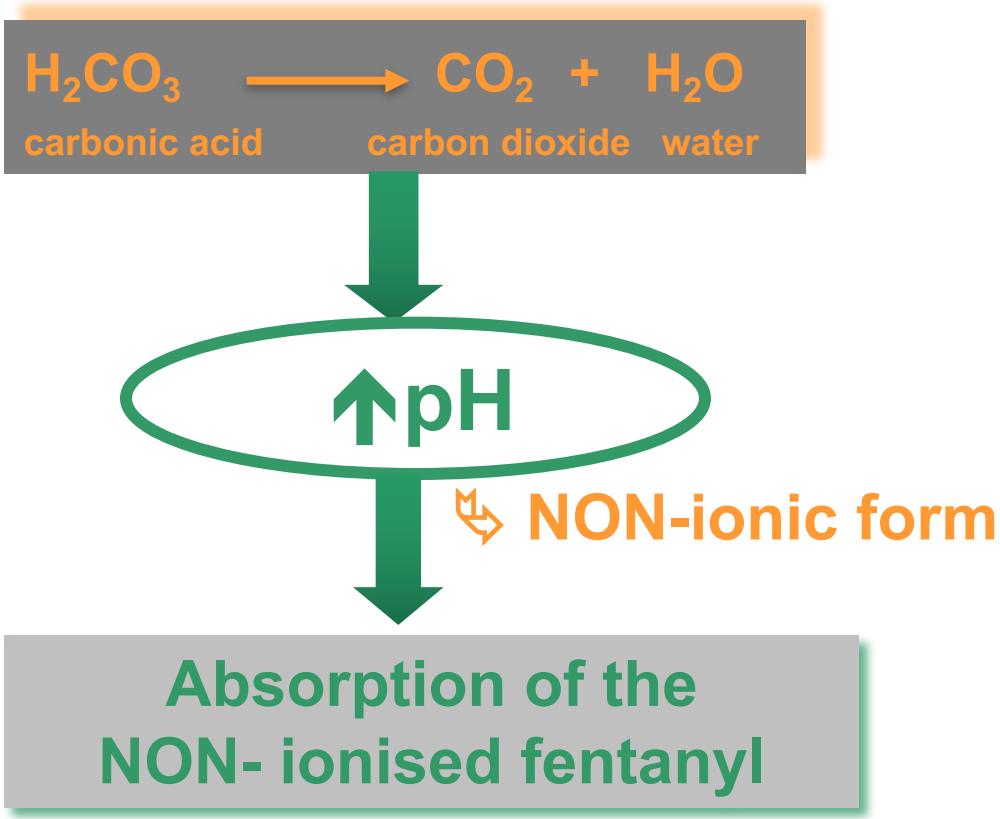
↓

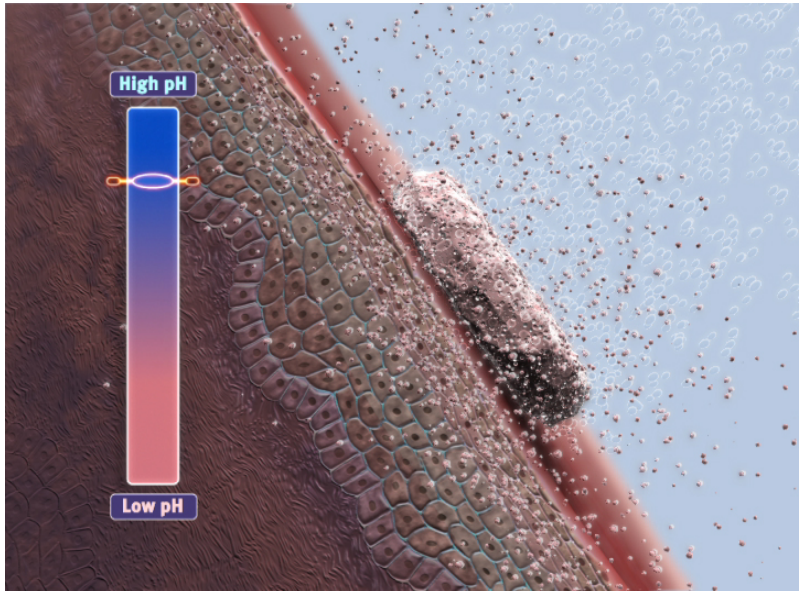
Dissolution of ionised fentanyl

*The OVT utilises an **effervescent reaction***

Enhancing Absorption

- Carbonic acid dissociates into CO_2 and H_2O
  CO_2 released out of solution or is absorbed across oral mucosa

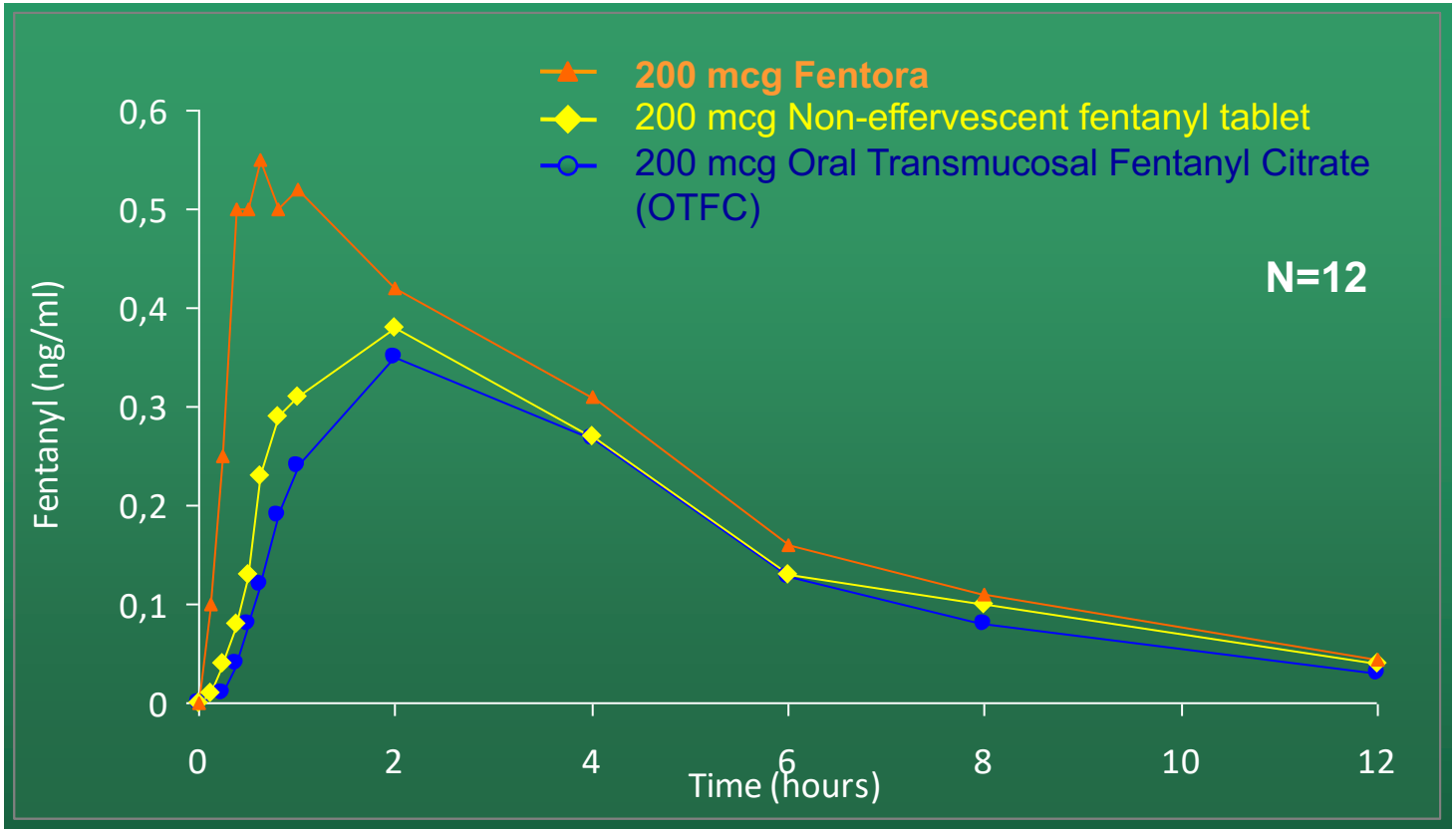




Durfee et al (2006). *Am J Drug Deliv,* 4: 1-5.

Fentanyl Serum Concentrations

Fentora™ vs Other Formulations



T_{max} occurred earlier and C_{max} and $AUC_{0-\infty}$ were greater with Fentora than with formulations not utilising OraVescent technology

1. Pather et al (2001). *Drug Deliv Tech,* 1: 54-57.
2. Durfee et al (2006). *Am J Drug Deliv,* 4: 1-5.

PK/PD studies submitted to the EMEA

Study ID	Study objective	Dose FBT
099-11* *M Darwish Clinl Ther May 2006; 28 (5): 715-725*	Bioavailability, dose proportionality, bioequivalence	270-1300 µg single dose
099-18* *M Darwish Clin Pharmacokinet 2005; 44 (12): 1279-1286*	Dose proportionality	200-1080 µg single dose
1026/BE/US* *M Darwish Clin pharmackinet 2006; 45 (8): 843-850*	Bioequivalence (4 x 100 µg tablets vs. 1 x 400 µg)	400 µg single dose
1027/PK/US* *M Darwish Clinical Therapeutics 2006; 28 (5): 707-714*	Dose proportionality	100-800 µg single dose
1028/BA/US* *M Darwish Clinical methodology 2007; 47: 1-8*	Bioavailability (buccal/ swallowed/i.v.)	400 µg 800 µg single dose
1029/PK/US* *M Darwish J of clin pharmacology 2007; 47: 56-63*	PK (single/multiple dose)	400 µg single dose, 400 µg x 4 for 5 days
1037/PK/US*	PK, dose proportionality	600-1200 µg single dose
099-16** *M. Darwish Clin Drug Invest 2007; 27 (9): 605-611*	Safety/tolerability Opioid-tolerant cancer patients with or without mucositis	200 µg single dose

**Healthy volunteers 18-45/55 years*

***Opioid-tolerant cancer patients ≥ 18 years with or without mucositis*

Pharmacokinetics Summary

- Absolute bioavailability is 65%, with 48% rapidly absorbed across the oral mucosa
- Early systemic exposure (C_{max}, t_{max}, $AUC_{0\text{-}tmax}$) was higher with Fentora™ vs. ACTIQ
- Fentora™ demonstrated linear pharmacokinetics from 100µg up to 1000µg
- Possible multiple units during titration

Efficacy and Safety Studies

Study number	Population	Study objective
099-14 ***R. Portenoy*** *The clinical Journal of Pain 2006; 22 (9): 805-811*	Opioid-tolerant patients with cancer and BTP	**Efficacy** and safety
3039/BP/US ***N Satklin*** *The journal of supportive oncology 2007; 15 (7): 327-334*	Opioid-tolerant patients with cancer and BTP	**Efficacy** and safety
POOLED DATA 9914-3039 ***POSTER*** *Perry Fine-* *American Academy of Pain Medicine, February 12-16, 2008, Orlando, Florida.*	Opioid-tolerant patients with cancer and BTP	Safety
099-15 ***POSTER*** *A.S. Weinstein, R. Thakur, J.Messina, F. Xie ASPE, Sep 6-9, 2007, Las Vegas, NV*	Opioid-tolerant patients with cancer and BTP	**Long term Safety** and efficacy open-label study

A Multicenter, Double-Blind, Placebo-Controlled Study of FBT for the Treatment of Breakthrough Pain in Opioid-Tolerant Patients with Cancer

Study 99-14

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

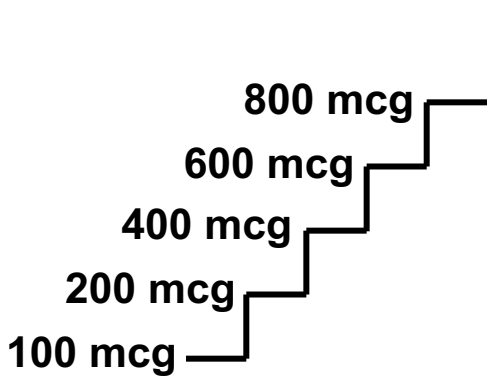
Objective

- **To evaluate the efficacy, safety and tolerability of Fentora™ in opioid-treated patients with cancer-related BTCP**

Study Design 9914

Study design:

- **Titration phase** : open-label phase
- **Efficacy phase** : randomised, double-blind placebo-controlled



Titrate to dose that effectively manages 2 consecutive BTP episodes

10 BTP episodes treated in a predetermined sequence with Fentora™ or placebo (7 Fentora™, 3 placebo)

F P F F F P F F F P

Visit 1	Visit 2	Visit 3	Visit 4
Screening	Open-label *Fentora*® dose-titration period	Randomized, double-blind treatment period	End of study or early termination
≈14 days	≈21 days	≈21 days	

Note: Patients were not allowed to titrate above 800 µg.

Successful dose: *satisfactory relief within 30 minutes, without unacceptable adverse effects, during the 2 consecutive BTP episodes.*

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

Study 9914: Criteria

Primary Endpoint

- **$SPID_{30}$**
  Sum of the patient Pain Intensity Differences (PID) measured at 15 and 30 minutes

Secondary Endpoints

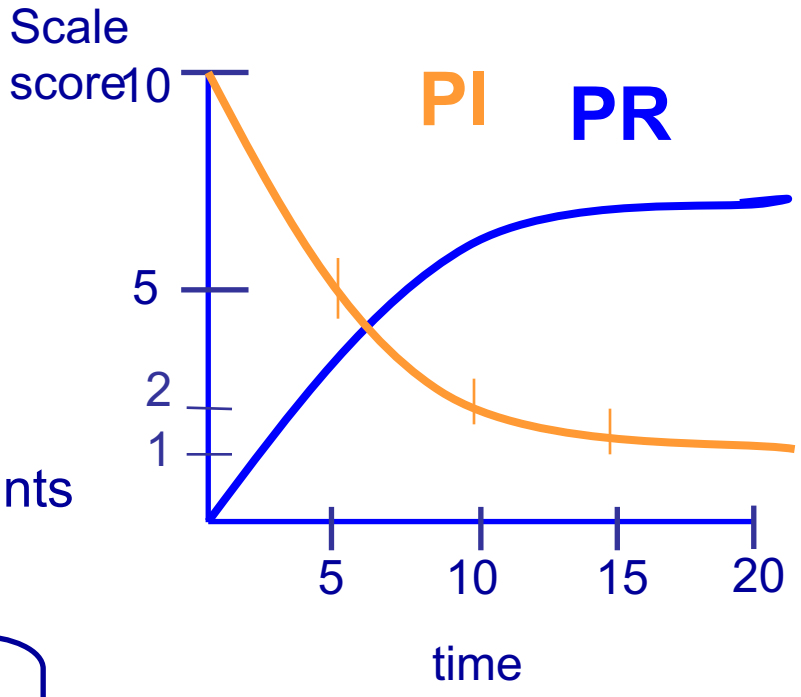
- **Pain Intensity (PI):**
  Measured on a 11-point numeric scale from 0 (no pain) to 10 (worst pain), recorded immediately before dosing (0 minutes) and at **15, 30, 45, and 60 minutes** after dosing
- **PID at each time and % of BTP with improvement of 33% & 50%**
- **Pain Relief (PR):**
  Measured on a 5-point numeric scale
  Assessed at **15, 30, 45, and 60** minutes after dosing
- **Total Pain Relief: TOTPAR**
- **Patient-rated global assessment of study drug performance (GMP),** measured on a 5-point scale
  Completed at 30, 60 minutes after dosing
- **Use of standard medication used for rescue**

R.Portenoy The clinical Journal of Pain 2006; 22 (9): 805-811

Definitions

Efficacy criteria

- **PID:** Pain Intensity Difference
- **SPID:**
  Sum of Pain Intensity Difference
- **TOTPAR:**
  the sum of PR scores at ≠ time points post dose;



Time min	PI	PID
0	10	na
5	5	5
10	2	8
15	1	9

SPID $_{15}$= 22

Study 9914- Key Inclusion Criteria

☺ Population
To be included

➢ **Opioid-treated patients with cancer-related BTP.**

- ***Cancer patients***: Histologically documented diagnosis of a malignant solid tumor or a hematologic malignancy with cancer-related pain
- Eastern Cooperative Oncology Group (ECOG) performance status rating ≤2, and a life expectancy ≥3 months
- ***Opiods treated patients***: Receiving 60-1000 mg morphine/day or 50-300 µg per hour transdermal fentanyl or opioid equivalent for at least a week for cancer-related pain
- ***BTCP***: Adult patients with **1-4 BTCP episodes** per day (defined as temporary flares of severe)

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

Study 9914: Results
Patient Demographics/ Baseline Characteristics

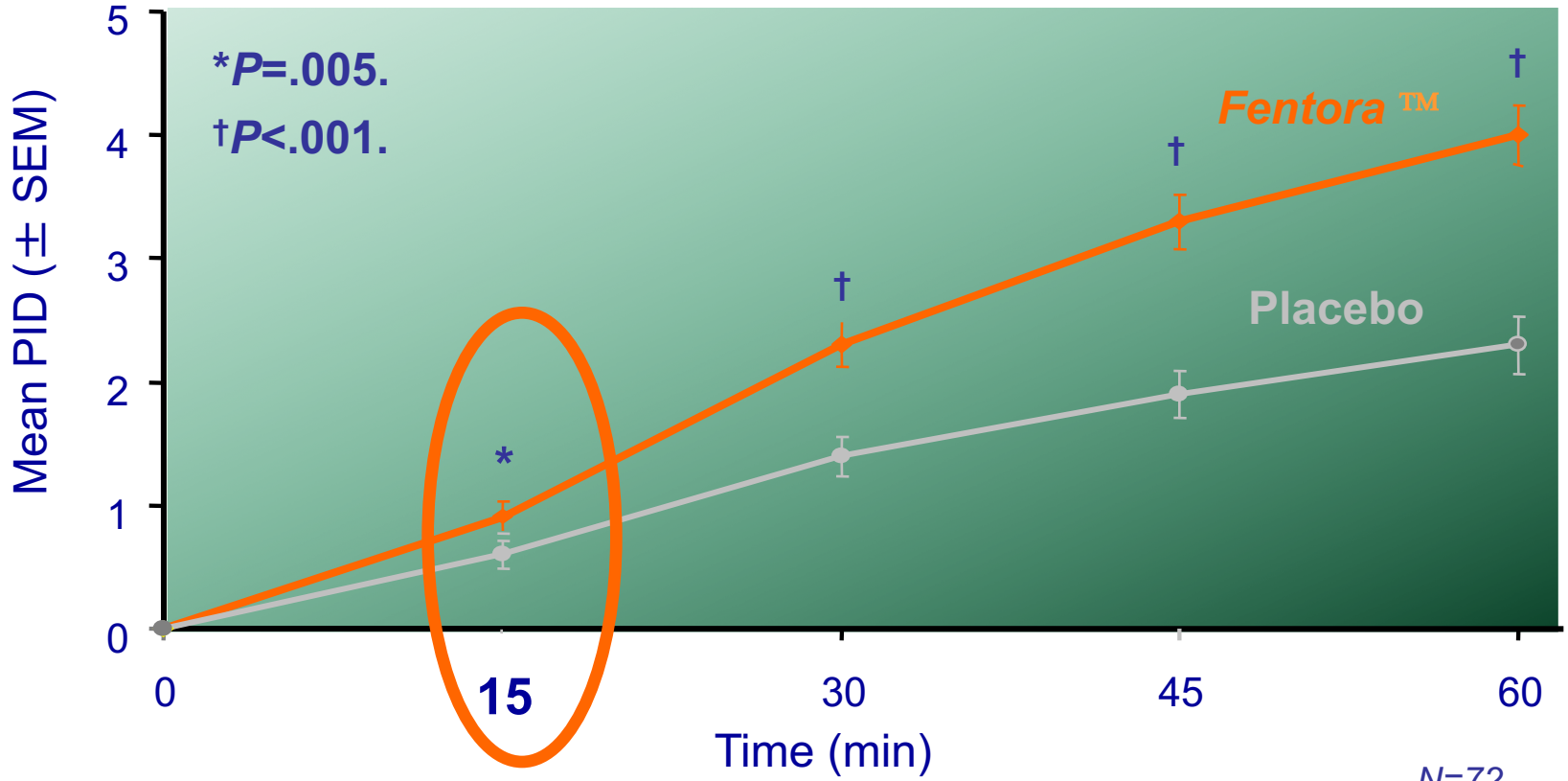
➢Type of Cancer

	N=123 n (%)
Lung	28 (23)
Breast	22 (18)
Haematological	12 (10)
Prostate	12 (10)
Unknown	9 (7)
Colorectal	9 (7)
Pancreatic	8 (7)
Gynaecological	6 (5)

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

Study 9914 results:
Mean Pain Intensity Difference (PID) Over Time

- $mSPID_{30}$ Fentora™ = 3.2 ± 2.6, Placebo = 2.0 ± 2.21 p<0.0001[1]



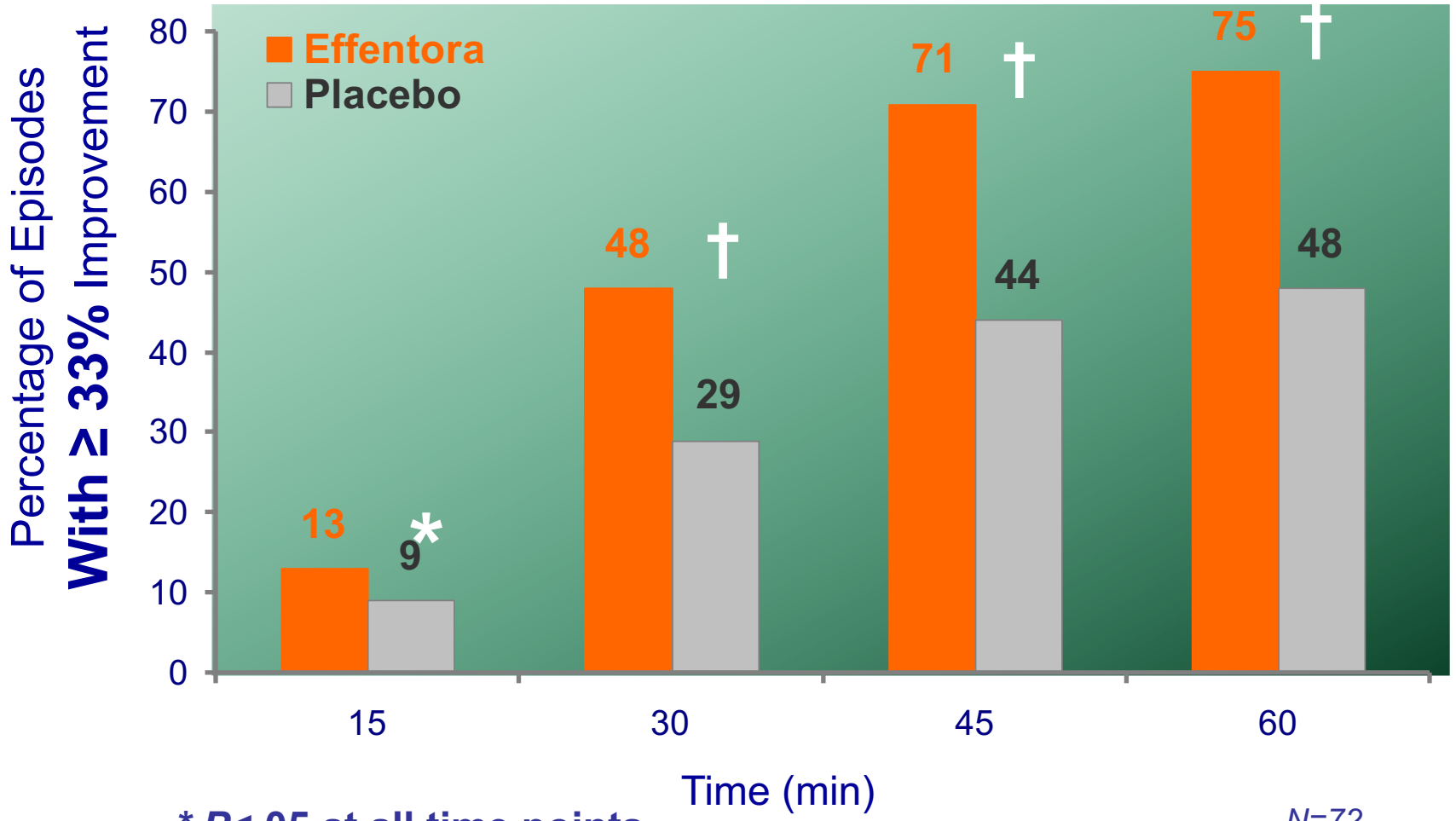
* p<0.05

† p<0,01

1- SmPC

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

Study 9914 Results:
Clinically Significant Change in Pain Intensity



* *P*<.05 at all time points

† P<0.0001

N=72

R.Portenoy *The clinical Journal of Pain 2006; 22 (9): 805-811*

A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety of Fentora™ in Opioid-Tolerant Patients with Cancer and Breakthrough Pain

Study 3039

N Satklin the journal of supportive oncology 2007; 15 (7): 327-334

Objective

- **To evaluate the efficacy and tolerability of Fentora™ for BTCP in opioid-tolerant patients with cancer-related chronic pain, expanding upon previous findings by examining the effects of Fentora™ versus placebo at both earlier and later time points following dosing**

Study 3039: Criteria

Primary Endpoint

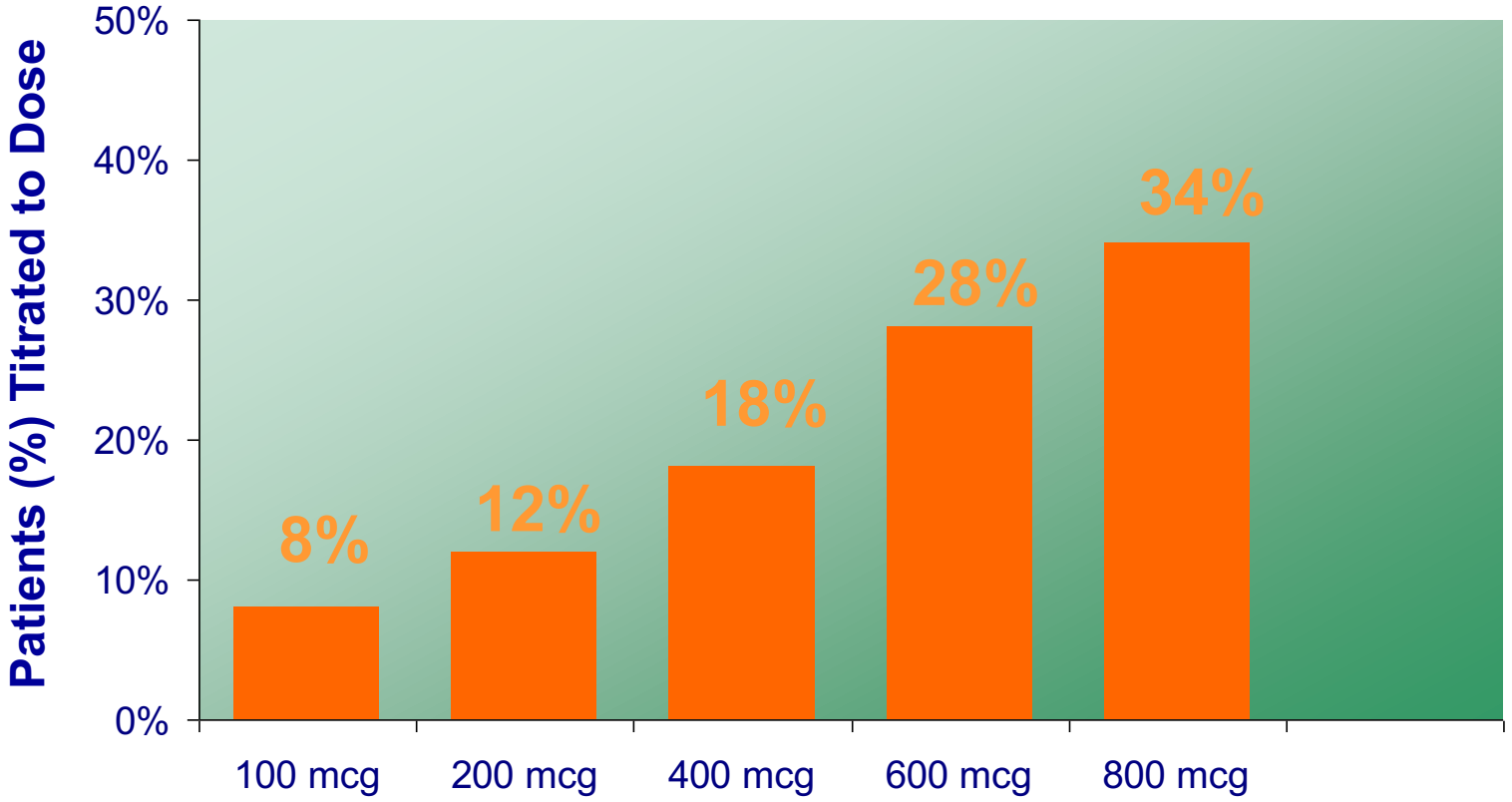
- **$SPID_{60}$**
  Sum of the patient Pain Intensity Differences (PID) measured from 5 to 60 minutes

Secondary Endpoints

- **Pain Intensity (PI):**
  Measured on a 11-point numeric scale from 0 (no pain) to 10 (worst pain), recorded immediately before dosing (0 minutes) and at **5, 10, 15, 30, 45, 60, 90, and 120 Minutes** after dosing
- **PID at each time and % of BTCP episodes with improvement of 33% & 50%**
- **Pain Relief (PR):**
  Measured on a 5-point scale, assessed at 15, 30, 45, and 60 minutes after dosing
- **Total Pain Relief: TOTPAR at 60, 90,** and 120 minutes
- **Patient-rated global assessment of study drug performance (GMP),** measured on a 5-point scale
  completed at 30, 60 minutes after dosing
- **Use of standard medication used for rescue**

Study 3039 results: Titration phase: Successful Dose of Fentora™

- **70%** of patients reached a successful dose

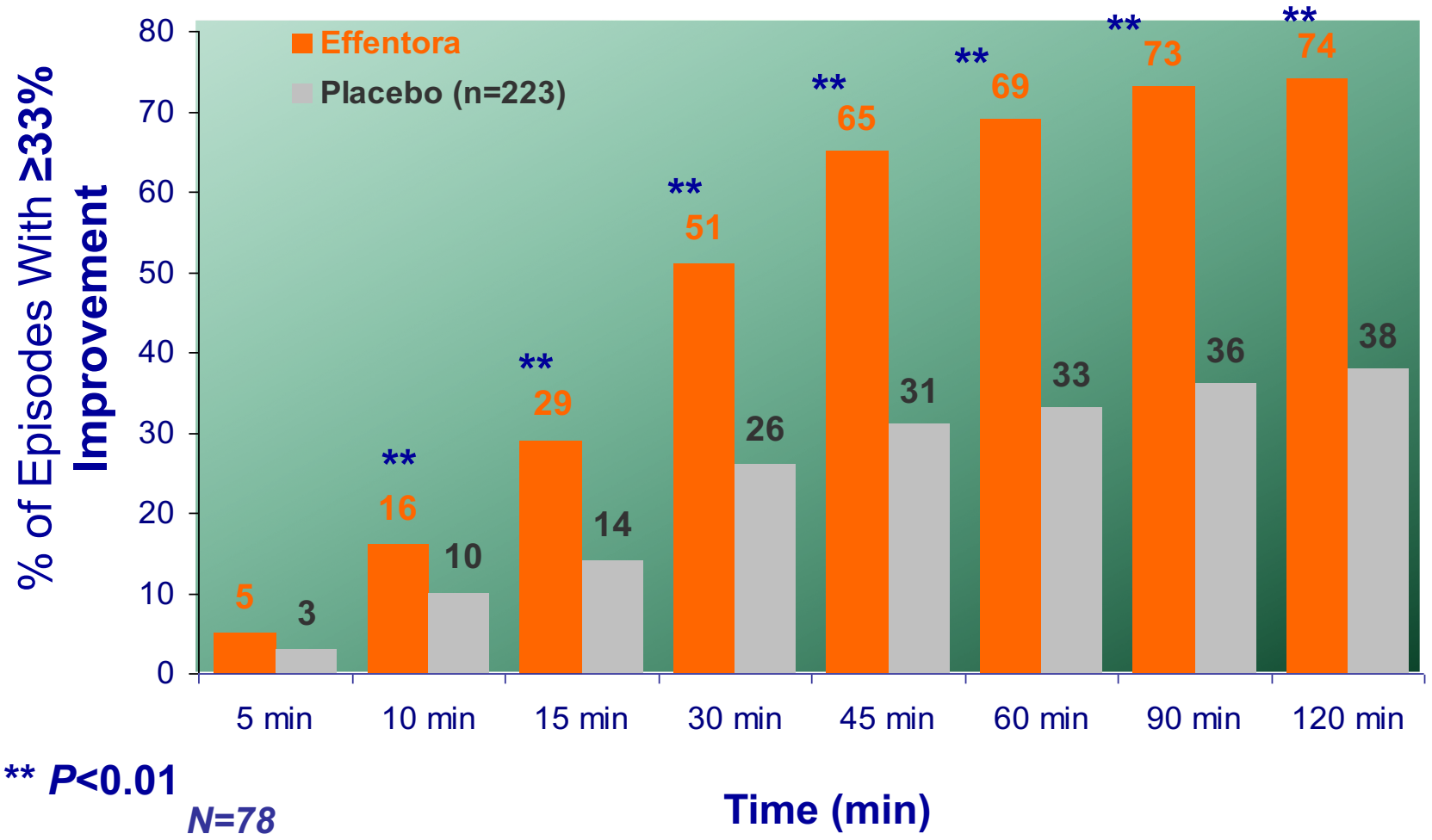


Successful dose =

The dose strength that provided adequate analgesia for 2 consecutive episodes of BTP without unacceptable adverse events.

N Satklin the journal of supportive oncology 2007; 15 (7): 327-334

Study 3039 results:
Clinically Significant Change in Pain Intensity



** *P*<0.01

N=78

N Satklin the journal of supportive oncology 2007; 15 (7): 327-334

Efficacy Studies conclusions

- **70%** of patients found a successful ***Fentora***™ dose in the range of 100µg to 800 µg
- ***Fentora***™ was consistently and significantly superior to placebo on all measures of efficacy
- Efficacy observed as early as **10 minutes** after taking ***Fentora***™ and increased through 120 minutes
- Episodes treated with placebo were **twice** as likely to require **rescue medication** as those treated with ***Fentora***™
- Adverse events were typical of those observed with opioids; no respiratory depression reported in clinical trial

Safety conclusions

- Most common adverse events were **typical of opioids**
- Most AEs were **mild to moderate** in severity
- **10% of patients** experienced at least one AE related to the tablet application
- The **most frequent AE** (≥10% patients) were the following:
  - Nausea, dizziness, vomiting,.
  - AE related to the application site were reported for 9% patients
- The incidence and type of adverse events **did not appear to be dose related**
- The rapid absorption of ***Fentora***™ did not appear to affect the type or severity of adverse events

EAPC, ESMO, NCCN recommendations: ROOs are preferred medication for BTcP

EAPC

- **Oral transmucosal fentanyl formulations** are more effective than immediate-release oral morphine and that intranasal fentanyl affords faster analgesia than the oral transmucosal formulation.

NCCN

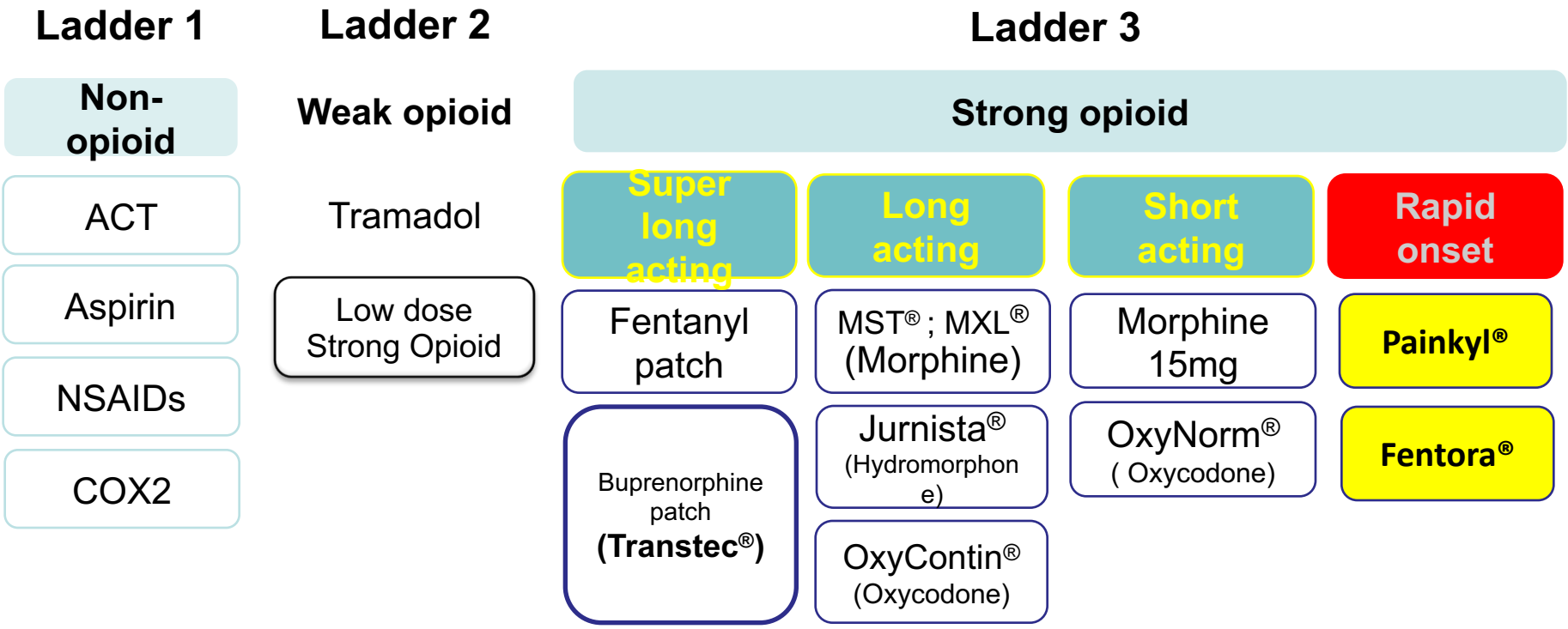
- **Consider rapidly acting transmucosal fentanyl** in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid.

ESMO

- Intravenous opioids; **buccal**, sublingual and intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating BTP episodes in respect to oral morphine.

Lancet Oncol. 2012; 13(2):e58–e68
Annals of Oncology 23 (Supplement 7): vii139–vii154, 2012
2014 NCCN

Opioid classification



FENTORA 適用症:

fentanyl buccal soluble tab 口頰錠

適用於18 歲以上，對正在使用日夜連續型(around-the-clock) 鴉片類藥物來治療癌症相關的持續性疼痛有耐藥性的癌症患者所發生的突發性疼痛(breakthrough pain)。所謂患者對日夜連續型鴉片類藥物有耐藥性，係指每日使用下列藥物:

at least 60 mg of oral morphine daily,
at least 25 mcg/hr. of transdermal fentanyl,
at least 30 mg of oral oxycodone daily,
at least 8 mg of oral hydromorphone daily,
at least 25 mg oral oxymorphone daily,

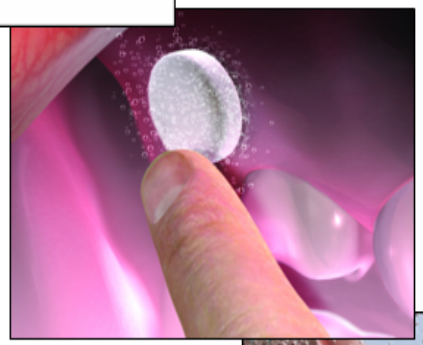
或每日使用具有等止痛劑量之其他鴉片類藥物。
病患在使用FENTORA 同時，必須規律性使用日夜連續型鴉片類藥物。

FENTORA
fentanyl buccal tablet

1. Peel it.

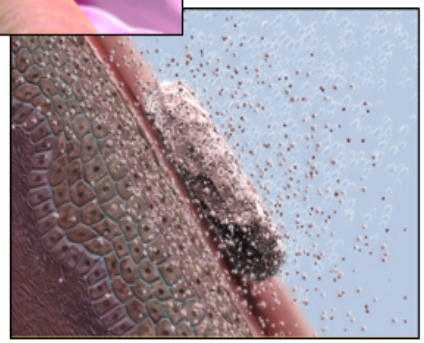
Patient bends and peels blister backing to expose tablet.*

放置於上頰及牙齦之間
(除此之外,也可將口頰錠置於舌下也能產生一樣的藥效)



2. Place it.

Patient **immediately** places entire tablet in the buccal cavity above a rear molar.



3. Feel it.

Tablet dissolves in approximately 14 to 25 minutes, without active administration.†

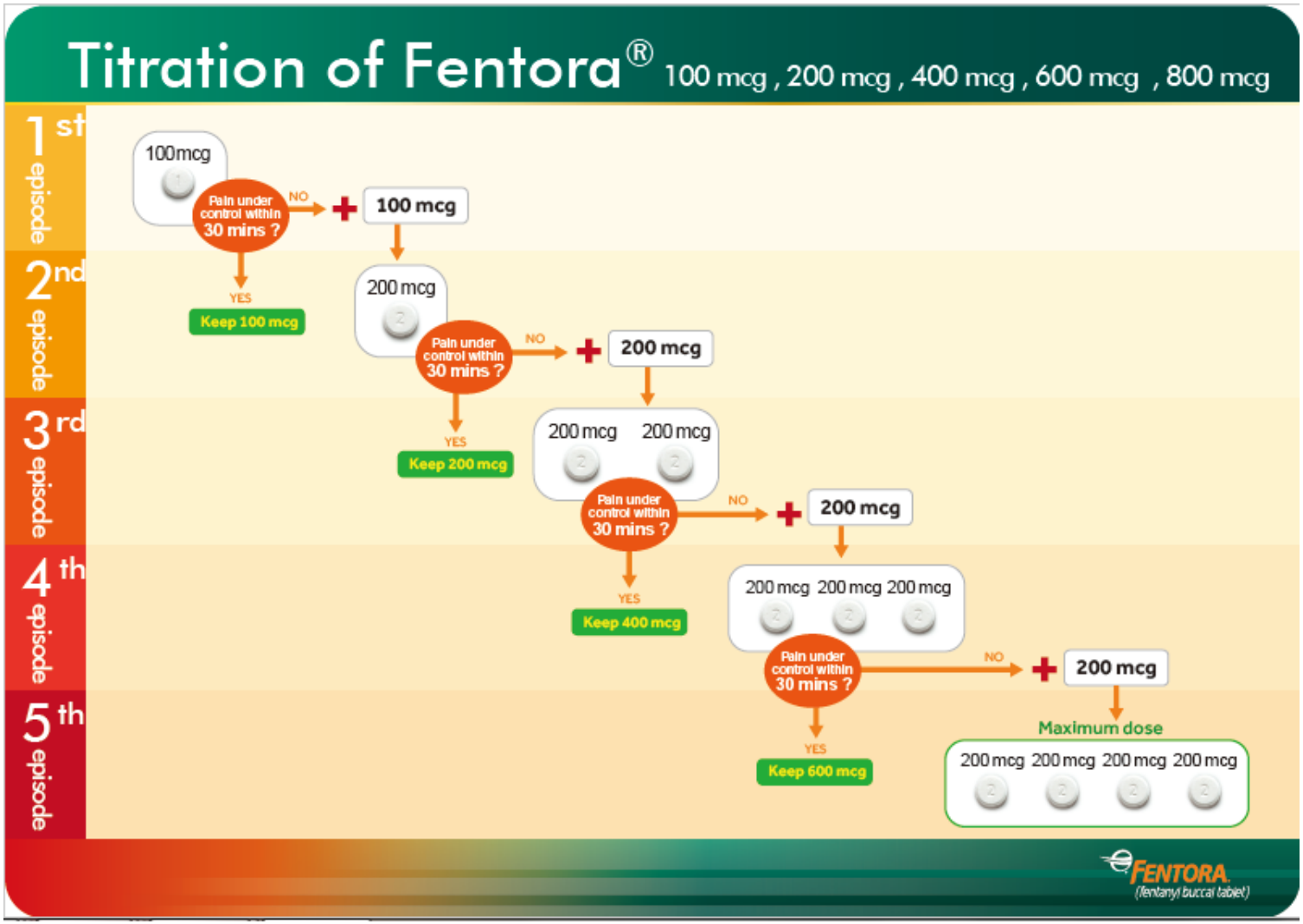
*Tablet should not be stored once removed from the blister package, as the tablet integrity may be compromised and risk of accidental exposure to a tablet can occur.

†If remnants from the tablet remain after 30 minutes, they may be swallowed with a glass of water.

FENTORA [package insert]. Frazer, PA: Cephalon, Inc.; 2007.

FENTORA
fentanyl buccal tablet

Titration


Titration of Fentora® 100 mcg , 200 mcg , 400 mcg , 600 mcg , 800 mcg
1st episode
100mcg
Pain under control within 30 mins ?
NO
100 mcg
YES
Keep 100 mcg
2nd episode
200 mcg
Pain under control within 30 mins ?
NO
200 mcg
YES
Keep 200 mcg
3rd episode
200 mcg 200 mcg
Pain under control within 30 mins ?
NO
200 mcg
YES
Keep 400 mcg
4th episode
200 mcg 200 mcg 200 mcg
Pain under control within 30 mins ?
NO
200 mcg
YES
Keep 600 mcg
5th episode
Maximum dose
200 mcg 200 mcg 200 mcg 200 mcg
FENTORA
(fentanyl buccal tablet)

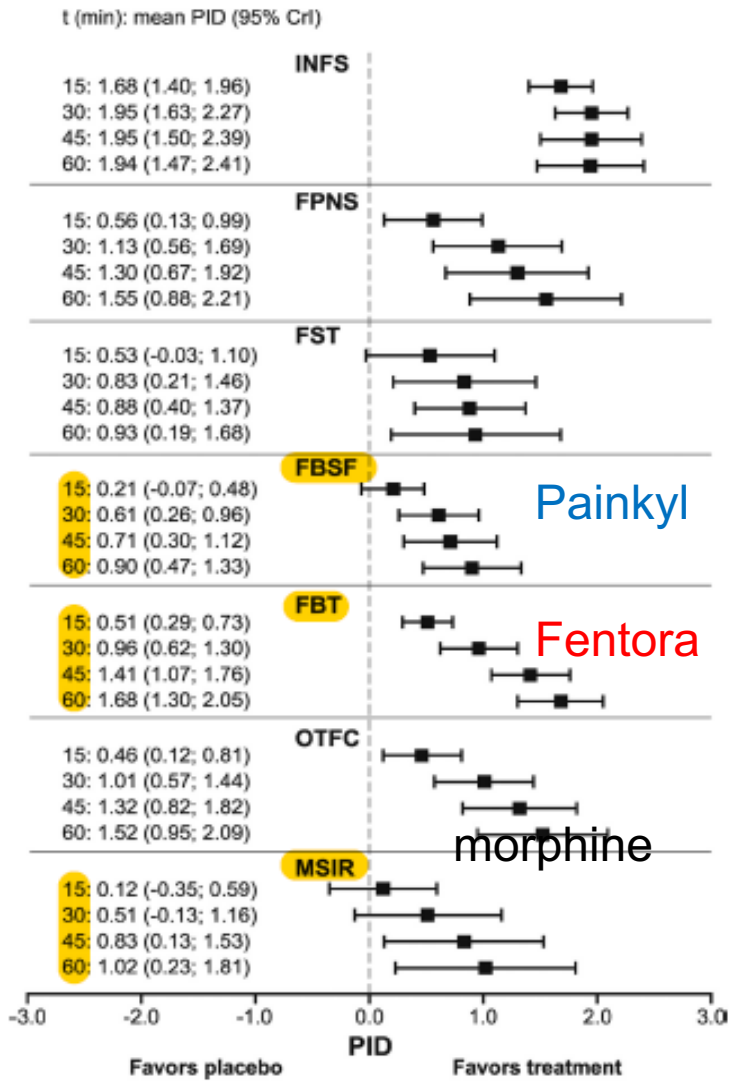
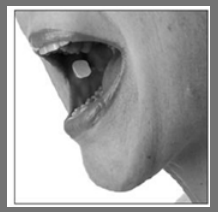
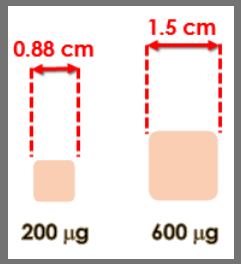
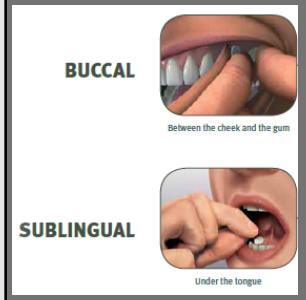


Fig. 3. PID of BTCP medications relative to placebo. PIDs relative to placebo were calculated for each medication by subtracting a pooled reference estimate of PID for placebo (derived from a fixed-effects meta-analysis of the results from the placebo-controlled trials included in the network meta-analysis). Pooled placebo data allow for standardization across studies. PID = pain intensity difference; BTCP = breakthrough cancer pain; CrI = credibility interval; INFS = intranasal fentanyl spray; FPNS = fentanyl pectin nasal spray; FST = fentanyl sublingual tablets; FBSF = fentanyl buccal soluble film; FBT = fentanyl buccal tablets; OTFC = oral transmucosal fentanyl citrate; MSIR = morphine sulfate immediate release.

ROOs meta-analysis

Zeppetella et al. JPSM 2014; 47: 772-784

藥品	劑量與健保價	劑型/投藥方式[1,2]	使用方法[1,2]	專利釋放技術[1,2]	外觀與大小
Painkyl	200mcg: 275元 400mcg: 550元 (275x2)	**FBSF: 口頰溶片** **黏貼於口頰** 	每次突發性疼痛發作時僅可給予一次劑量，距離下次給藥應至少間隔2小時。	BEMA® (BioErodible MucoAdhesive) Film Technology 	
Fentora	100mcg: 220元 200mcg: 250元 400mcg: 500元 (250x2)	**FBT: 口頰錠** **含於口頰與舌下兩種給藥方式** 	每次突發性疼痛發作時先給予一次劑量，30分鐘後若無改善可再給予一次相同劑量，距離下次疼痛應間隔4小時。	OraVescent® drug delivery Technology