

# Long-Term Dosing, Safety, and Tolerability of Fentanyl Buccal Tablet in the Management of Breakthrough Pain in Opioid-Tolerant Noncancer Patients

PT 221

Srinivas R. Nalamachu, MD<sup>1</sup>; John Messina, PharmD<sup>2</sup>; Fang Xie, PhD<sup>2</sup>; Lynn R. Webster, MD<sup>3</sup>  
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## INTRODUCTION

- Breakthrough pain (BTP) is a transitory exacerbation, or flare, of moderate-to-severe pain that occurs in patients with persistent pain otherwise controlled with opioids.<sup>1,4</sup>
- Fentanyl buccal tablet (FBT) is indicated for the management of BTP in patients with cancer who are already receiving and are tolerant to opioid therapy for their underlying, persistent cancer pain.<sup>5</sup>
- Short-term clinical studies have shown the efficacy and generally good tolerability of FBT when used to treat BTP in opioid-tolerant patients with chronic cancer<sup>6,7</sup> or noncancer pain.<sup>8,9</sup>
- Unlike patients with cancer and BTP, who may have a limited life expectancy, patients with chronic noncancer pain and BTP are likely to require treatment for prolonged periods.
- Currently, limited data are available concerning the long-term use of supplemental opioids for the management of BTP.

## OBJECTIVE

- To evaluate the dosing, safety, and tolerability of FBT across four phase 3 clinical studies of opioid-tolerant patients with BTP who were taking around-the-clock (ATC) opioids for chronic noncancer pain.

## METHODS

- Data were combined from four phase 3 studies of FBT (**Table 1**) with similar patient inclusion/exclusion criteria:
  - The studies enrolled opioid-tolerant patients aged 18 to 80 years with persistent, noncancer pain experiencing 1 to 4 BTP episodes per day that were only partially relieved with supplemental opioid medication.
  - Opioid tolerance was defined as  $\geq 60$  mg of oral morphine/day,  $\geq 25$   $\mu$ g of transdermal fentanyl/hour,  $\geq 30$  mg of oxycodone/day,  $\geq 8$  mg of hydromorphone/day, or an equivalent dose of another opioid as a stable ATC dose for  $\geq 7$  days prior to study entry.
- All studies began with a screening phase followed by an open-label titration phase.
  - FBT was titrated to a successful dose for each individual patient, i.e., the single dose from 100  $\mu$ g to 800  $\mu$ g that relieved pain for at least 2 of 3 BTP episodes, without requiring a second dose or the use of supplemental medication, and without resulting in unacceptable adverse events (AEs).
  - In studies 1 to 3, patients then either entered a double-blind treatment phase immediately, or following a 1-month open-label phase. The common feature of double-blind treatment was a randomized sequence of 9 tablets (6 FBT, 3 matching placebo) utilized to treat 9 episodes of BTP.
  - In study 4, patients continued to take their already identified successful dose of FBT throughout an open-label treatment period, adjusted when there was clinical need.

**Table 1. Clinical Studies of FBT Contributing to the Integrated Data Analysis**

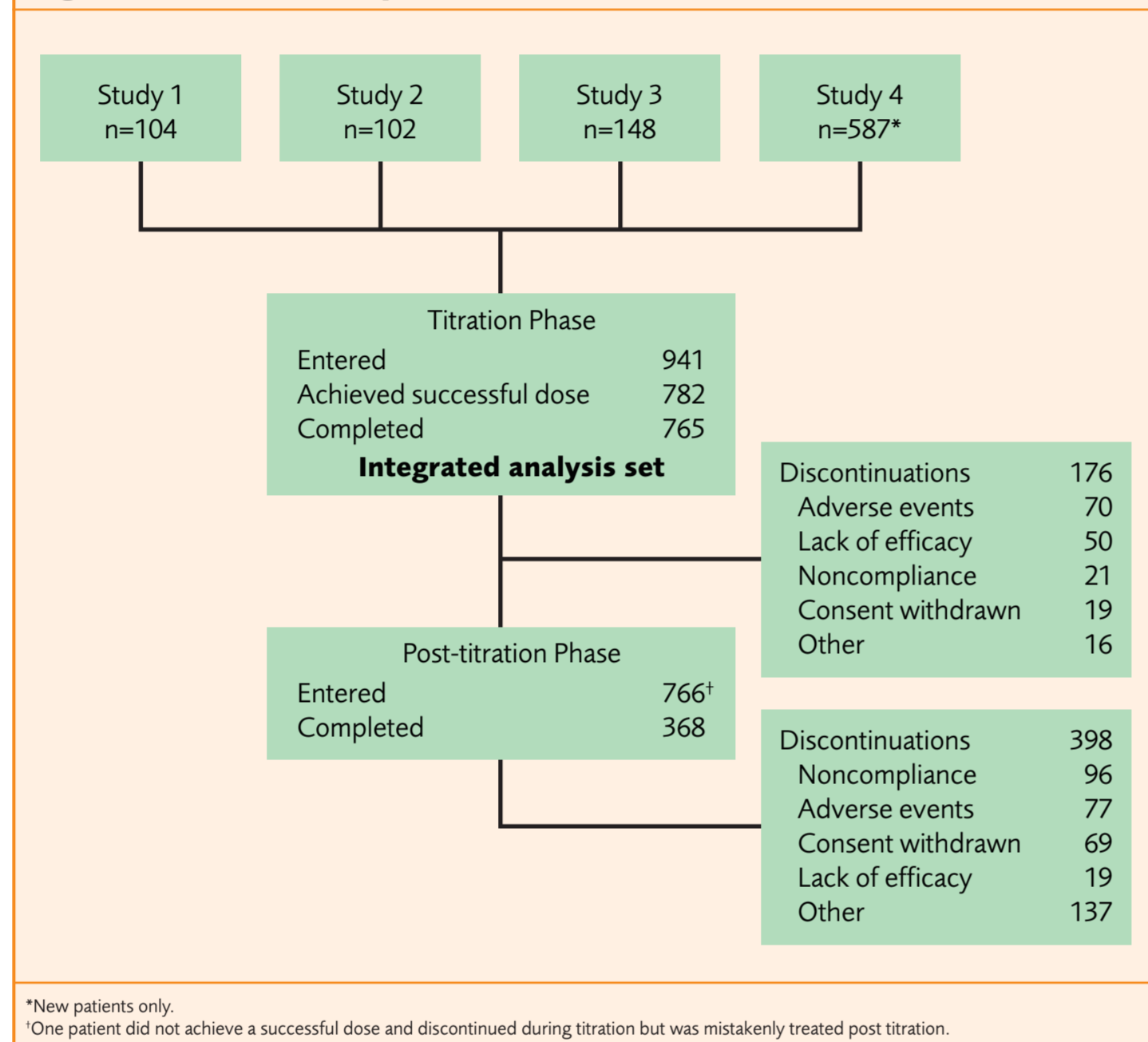
Study Design	Patient Population	Patients Treated With $\geq 1$ FBT Dose	Citation
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FBT=fentanyl buccal tablet; OA=osteoarthritis; DPN=diabetic peripheral neuropathy; PHN=postherpetic neuralgia; CRPS=complex regional pain syndrome.

## RESULTS

- 941 patients were included in the integrated analysis (**Figure 1**).
- 83% (782/941) of patients achieved a successful dose, and 81% (765/941) completed the titration phase.
- 766 patients took  $\geq 1$  dose of FBT after titration and constituted the post-titration analysis set.

**Figure 1. Patient Disposition**



- Baseline demographics were similar across the 4 studies (**Table 2**).

**Table 2. Baseline Patient Demographics and Disease Characteristics**

	Total (N=941)
Mean age (SD), y	48.7 (9.86)
Gender, n (%), male/female	407 (43) / 534 (57)
Race, n (%), white/black/other	874 (93) / 47 (5) / 20 (2)
Primary pain diagnosis	
Back pain	518 (55)
Traumatic injury	90 (10)
Osteoarthritis	54 (6)
Complex regional pain syndrome	53 (6)
Diabetic peripheral neuropathy	39 (4)
Chronic headache	34 (4)
Neck pain	16 (2)
Fibromyalgia	12 (1)
Postherpetic neuralgia	5 (<1)
Other	120 (13)
Pathophysiology of the BTP*	
Predominantly neuropathic	275 (29)
Predominantly nociceptive	287 (30)
Mixed (neuropathic/nociceptive)	273 (29)

\*Not collected for study 1 (n=104).

- The most common chronic pain conditions were back pain (n=518 [55%]), traumatic injury (n=90 [10%]), osteoarthritis (n=54 [6%]), and complex regional pain syndrome (n=53 [6%]).
- Patients had multiple comorbid conditions: for example, neurological (77%), psychiatric (73%), cardiovascular (58%), respiratory (40%), and endocrine (35%) abnormalities.
- As was consistent with study inclusion criteria, all patients were using ATC opioids for their persistent pain and supplemental opioid medication for BTP (**Table 3**).
  - 99% of patients were also taking medications for conditions other than pain.

**Table 3. Doses of Around-the-Clock (ATC) and Supplemental Pain Medications at Study Entry: Integrated Analysis Set**

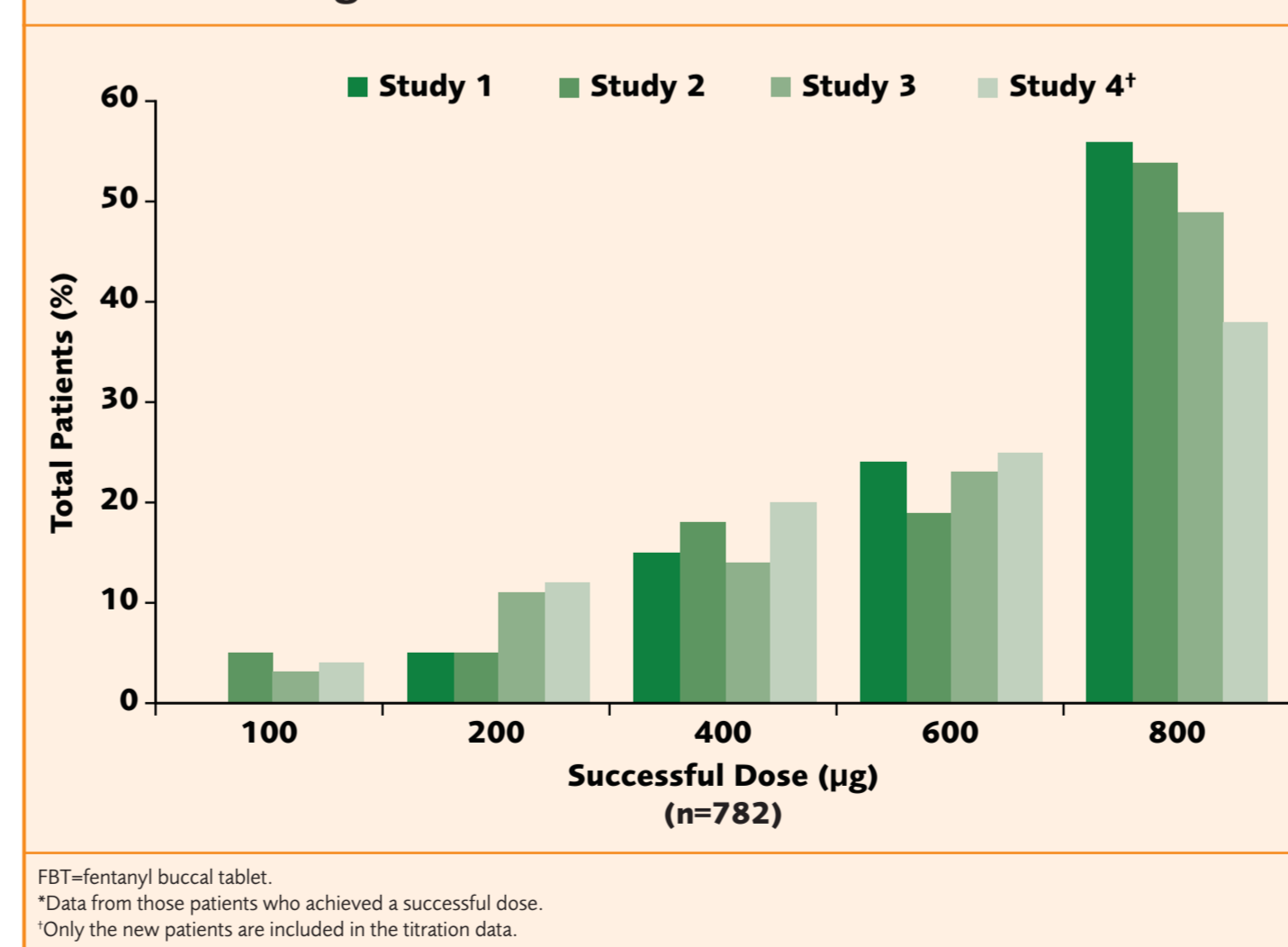
	Oral Opioids (n=688)	Transdermal Fentanyl (n=223)	Intrathecal Medications (n=30)*
ATC medication dose, <sup>†</sup> mg/d morphine equivalents			
Mean (SD)	211.1 (209.5)	209.3 (139.8)	–
Median (range)	120.0 (15.0, 2160.0)	180.0 (60.0, 1440.0)	–
Supplemental medication dose, <sup>‡</sup> mg/BTP episode morphine equivalents			
Mean (SD)	27.0 (27.3) <sup>§</sup>	31.8 (102.0)	35.2 (47.6) <sup>  </sup>
Median (range)	20.0 (1.3, 240.0)	20.0 (0.5, 1500.0)	20.0 (5.0, 192.0)

\*ATC dose was not summarized for patients using intrathecal opioids since these opioids were not converted to morphine equivalents.  
<sup>†</sup>Frequently used ATC medications included oxycodone, fentanyl, and morphine.  
<sup>‡</sup>Frequently used supplemental medications included oxycodone, hydrocodone, and fentanyl citrate.  
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## FBT Dosing and Exposure

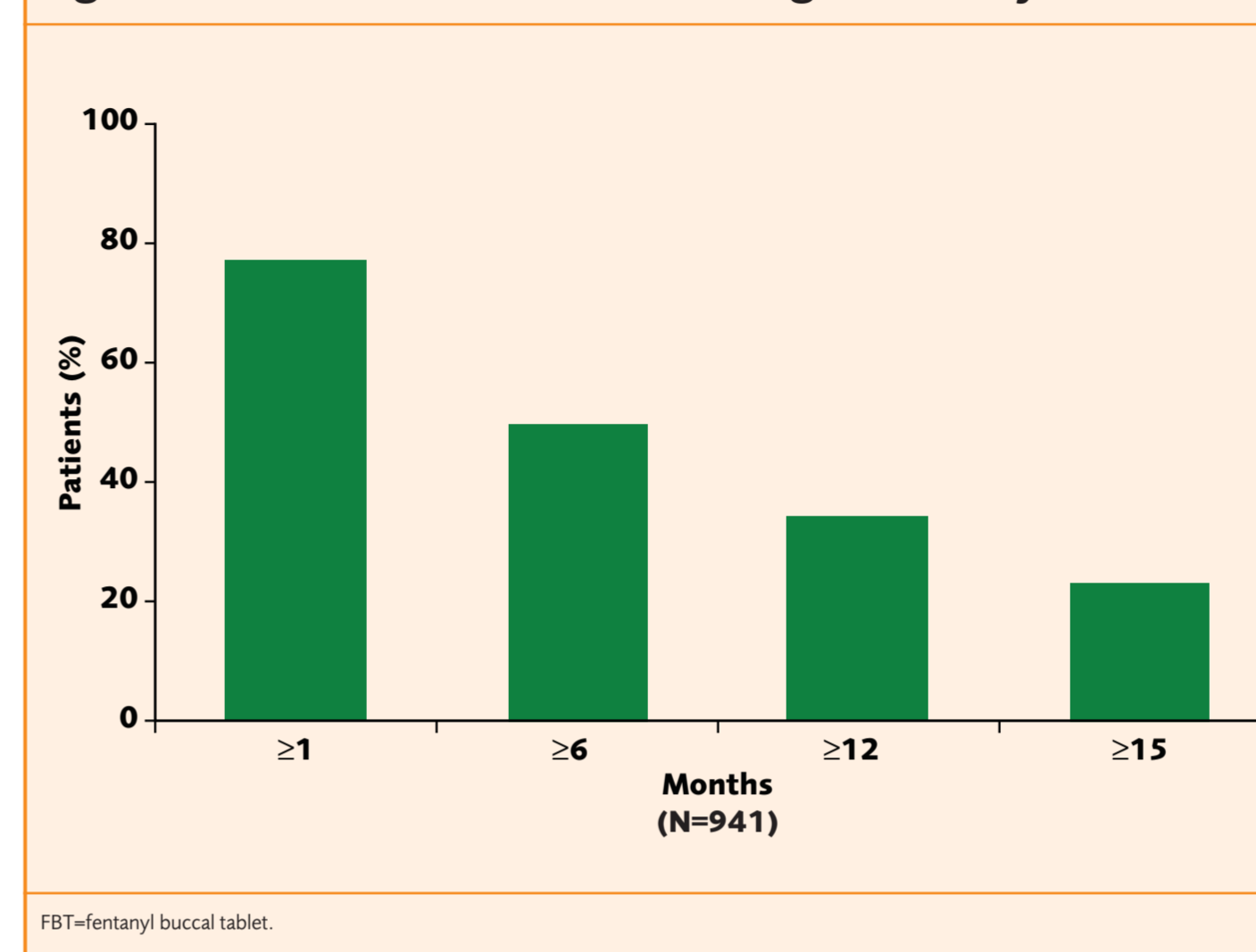
- During the titration period, 782 of 941 (83%) of patients achieved a successful dose of FBT.
  - In the majority of cases, the successful dose of FBT was 600  $\mu$ g (187/782 patients; 24%) or 800  $\mu$ g (338/782 patients; 43%) (**Figure 2**).

**Figure 2. Distribution of Successful Doses of FBT Identified During Titration Across the 4 Phase 3 Clinical Studies\***



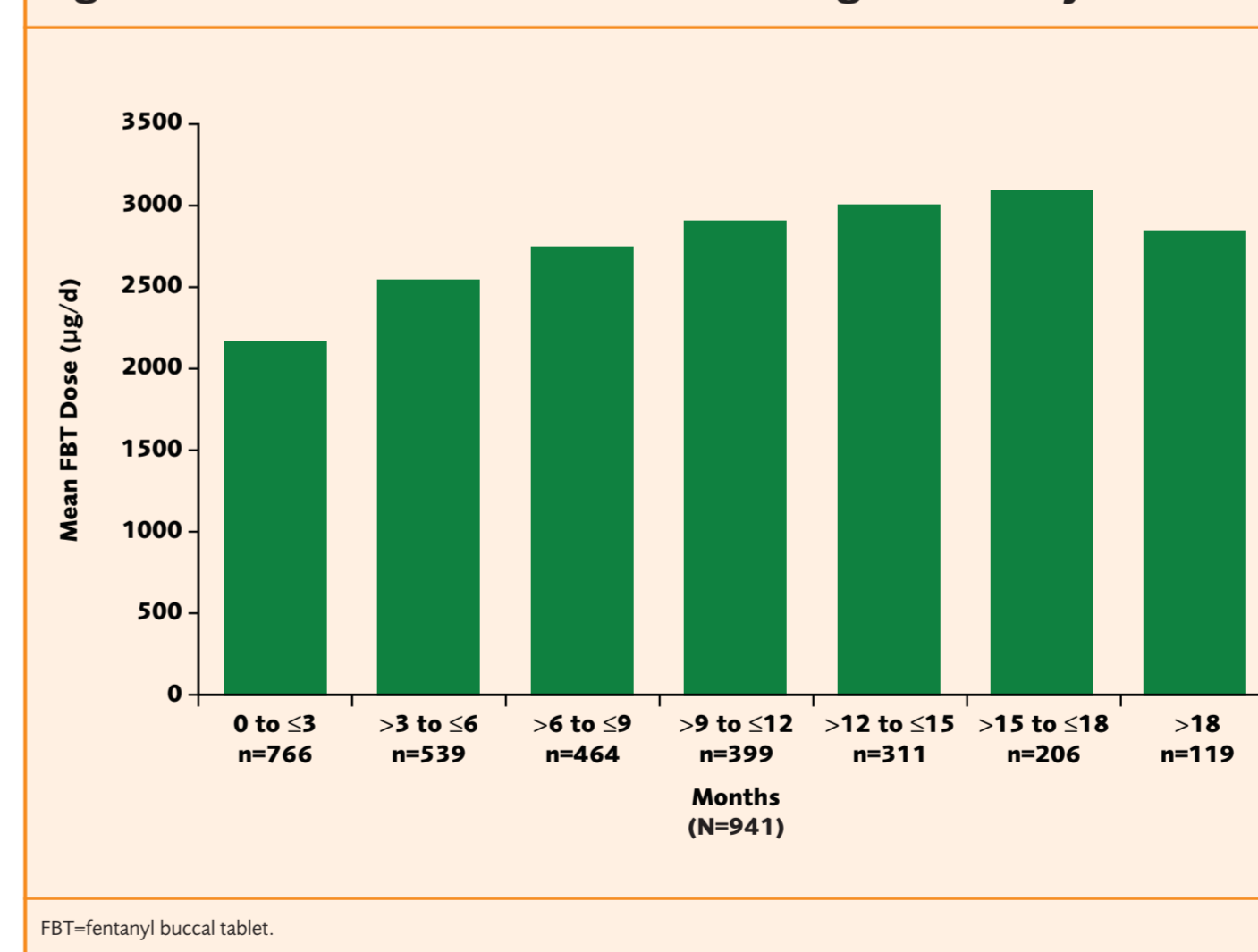
- Mean treatment duration for patients included in the analysis was nearly 8 months (241.3 days), amounting to a total exposure of 621.6 patient-treatment years (**Figure 3**).
  - Almost one quarter of the patients (23%) were treated for  $\geq 15$  months.

**Figure 3. FBT Treatment Duration: Integrated Analysis Set**



- Mean FBT dose increased over the 18-month analysis period, from 2161.9  $\mu$ g/day in the first 3 months to 2830.4  $\mu$ g/day in the last 3 months, corresponding to an approximate increase of 1 tablet of FBT per day (**Figure 4**).
  - 33% of patients had their FBT dose increased at least once.
  - Dose increases occurred more frequently during the first 3 months.

**Figure 4. Mean FBT Dose Over Time: Integrated Analysis Set**



- Increases in ATC dose paralleled increases in FBT dose.
  - Over the 18 months of the analysis period, the FBT daily dose remained at approximately 60% of the total daily opioid (FBT + ATC) dose.

## Safety and Tolerability

- Overall, 85% of patients (802/941) had  $\geq 1$  AE (**Table 4**).
  - The most frequent AEs were generally those commonly associated with opioids.
  - The frequency of the most common AEs did not appear to be related to FBT dose.

**Table 4. Adverse Events Experienced by  $\geq 10\%$  of Patients: Integrated Analysis Set**

Adverse Events	Number (%) of Patients (N=941)
Nausea	222 (24)
Vomiting	114 (12)
Dizziness	107 (11)
Back pain	105 (11)
Headache	100 (11)
Somnolence	95 (10)

Adverse events experienced by  $\geq 5\%$  to  $<10\%$  of patients were constipation, arthralgia, pain in extremity, urinary tract infection, peripheral edema, nasopharyngitis, diarrhea, upper respiratory tract infections, depression, insomnia, sinusitis, fatigue, and bronchitis.

- In general, AEs associated with opioid use occurred early in the course of treatment:
  - Median time to onset was often within the first 7 days of treatment, with the exception of constipation (102 days) and vomiting (54 days).
  - Median duration was  $\leq 2$  days, except for constipation (median duration 10.5 days).
  - Patients with these AEs generally had only 1 occurrence.
- The incidence of AEs decreased over time:
  - 69% of patients experienced  $\geq 1$  AE from 0 to 3 months; 47% of patients from 15 to 18 months.
  - The decrease may be related to a decrease in patient reporting of AEs, or a selection bias (patients remaining in the study may have been less prone to experiencing AEs).
- 116 patients (12%) had application-site AEs:
  - The majority (87%) resolved; others were ongoing at the time of analysis.
  - 11 patients (1%) discontinued because of application-site AEs.
  - Application-site AEs appeared more frequently in women (15%) than men (9%).
- 20 patients (3%) reported drug withdrawal syndrome:
  - Investigators considered the event to be related to FBT in 11 patients; in 5 of these patients the drug withdrawal was severe.
- 129 patients (14%) had  $\geq 1$  serious AE:
  - 6 patients died from causes unrelated to FBT (3 myocardial infarction, 2 cardiac arrest, 1 pneumonia).
  - 10 patients had serious AEs associated with an opioid overdose; all 10 patients recovered with no residual effect.
- 147 patients (16%) withdrew from the studies because of AEs.
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## CONCLUSIONS

- This analysis provides valuable clinical insight into the long-term dosing, safety, and tolerability of FBT in a large population of opioid-tolerant patients with chronic noncancer pain and BTP.

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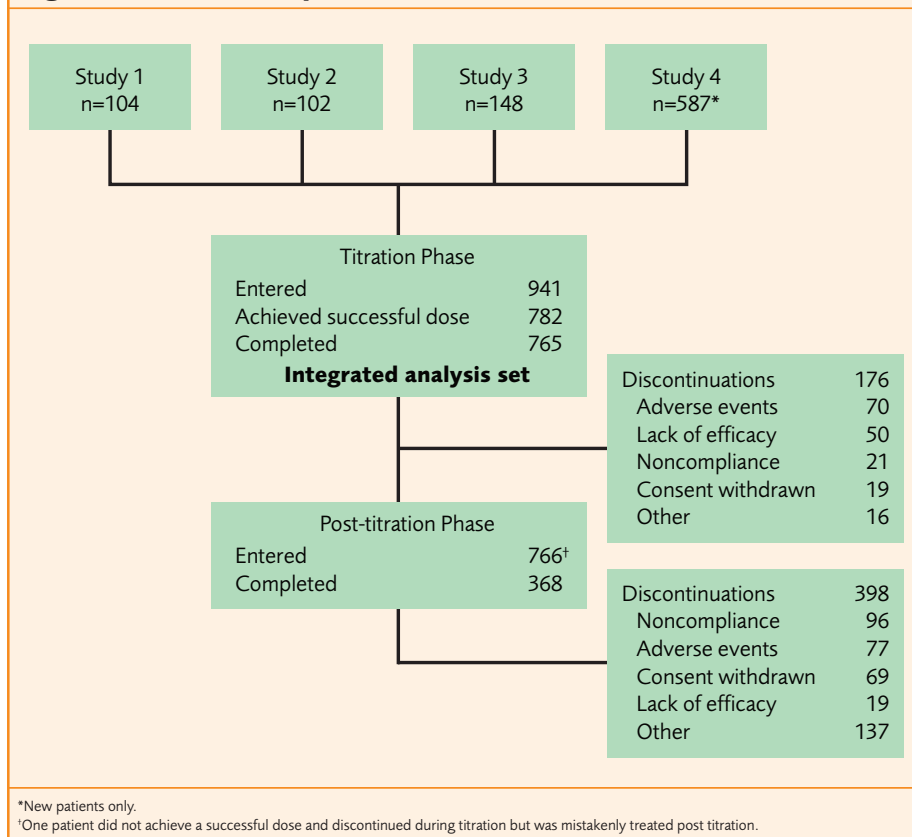
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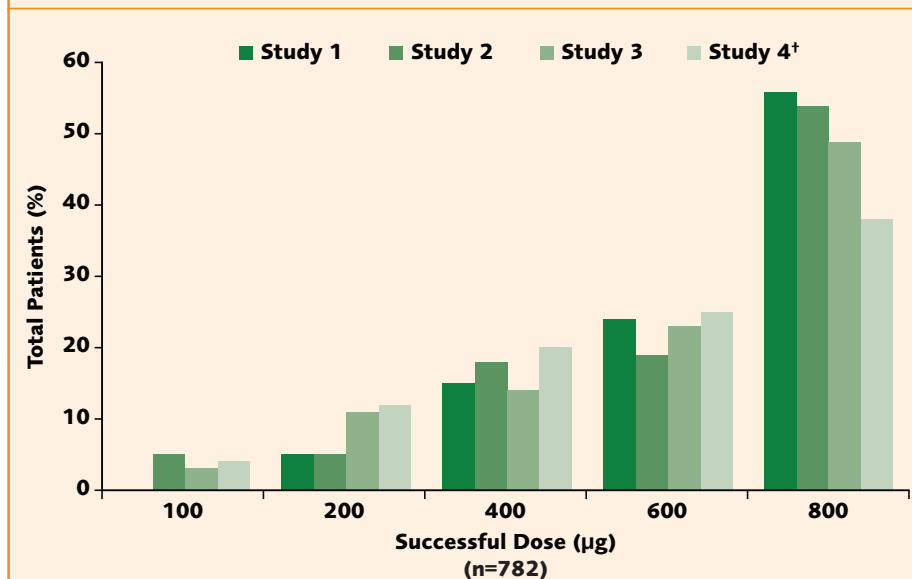
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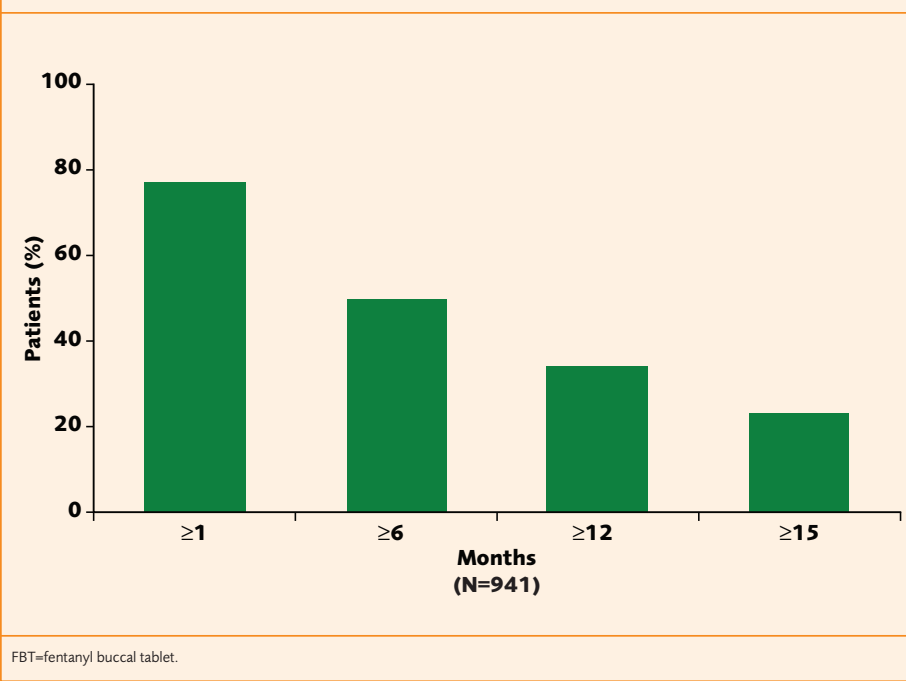
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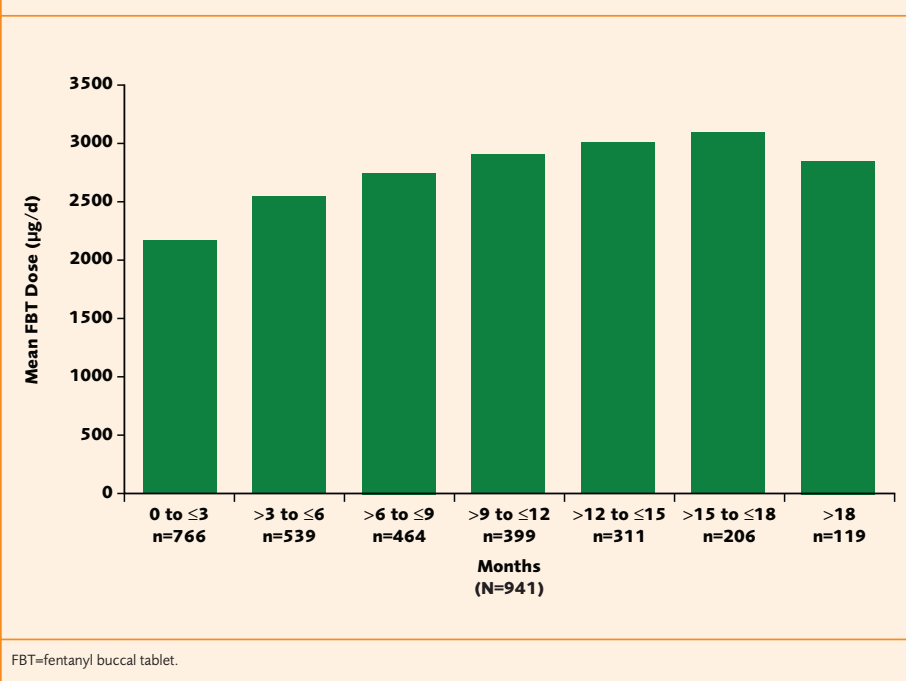
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