

Efficacy and tolerability of sublingual fentanyl in opioid-tolerant cancer patients with breakthrough pain: interim findings from two long-term, Phase III multi-centre studies

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Background

- Breakthrough cancer pain (BTcP) is a transitory exacerbation of pain in a background of otherwise controlled persistent pain.¹
- BTcP is a commonly occurring clinical problem and affects approximately two-thirds of patients with malignant disease.^{1,2}
- It is characterised by pain that is of rapid onset, short duration and severe intensity.³
 - Therefore, fast-acting, effective analgesics are crucial for successful treatment of BTcP.³
- Many immediate-release opioids, such as morphine, are often not ideal for the treatment of BTcP, as the onset of action can be too slow to treat the peak intensity of the pain episode.³
- Sublingual fentanyl citrate (SLF) is a new formulation of fentanyl citrate developed for the management of BTcP in opioid-tolerant patients.
- The pharmacokinetics of SLF indicate that it is rapidly absorbed,⁴ and therefore suggest that it should be well suited to the treatment of BTcP.

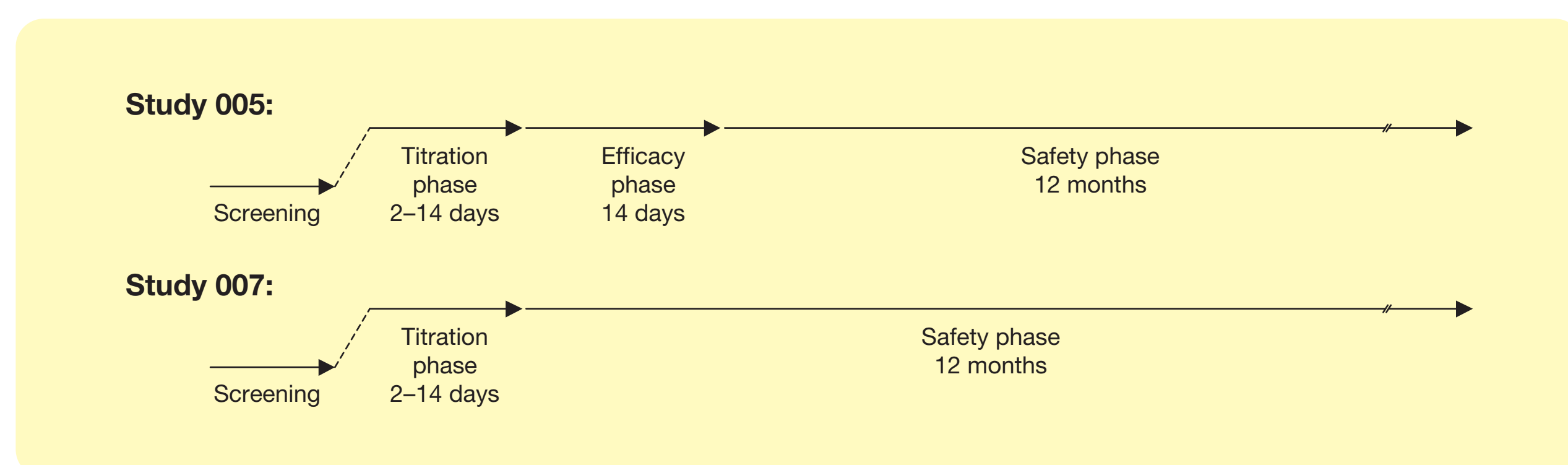
Objectives

- The objectives of these long-term studies were to:
 - compare the efficacy of SLF with placebo in the treatment of BTcP in opioid-tolerant patients
 - assess the long-term safety of SLF in this patient group.

Methods

- US-based, Phase III, multi-centre, multiple-dose studies.
- Both studies comprised a 2-week, open-label titration phase and a non-randomised, long-term open-label phase of ≤ 12 months (Figure 1).
 - In study 005, following titration and prior to the safety phase, patients completed a 2-week, randomised, double-blind, placebo-controlled efficacy phase.

Figure 1. Study design



Study population

- Opioid-tolerant male and female cancer patients aged >17 years were recruited.
- Patients were regularly experiencing at least one but not more than four episodes of BTcP per day, while receiving a stable, fixed-schedule opioid regimen equivalent to 60–1000 mg/day oral morphine or receiving transdermal fentanyl equivalent to 50–300 $\mu\text{g}/\text{h}$.
- Patients experiencing uncontrolled or rapidly escalating pain were excluded. Other exclusion criteria included: any clinical condition that could interfere with study drug administration and evaluations; anti-neoplastic therapy within 2 weeks of study entry that could influence pain assessment; any investigational drug within 30 days of study entry; allergy or contraindications to fentanyl.

Treatment

- During the open-label titration, the dosage of SLF was titrated upwards from 100 μg to a maximum of 800 μg , until a single stable dose was identified that successfully treated all BTcP episodes for 2 consecutive days.
- During the double-blind efficacy phase (study 005), patients received 7 doses of SLF (at the stable dose determined in the titration phase) and 3 of matching placebo, in a random order, over 10 BTcP episodes.
- During the safety phase, patients received doses of SLF for BTcP episodes as required.
- Consecutive doses of study medication were separated by ≥ 2 hours.
- Rescue medication was permitted.

Efficacy and safety evaluation

- Pain intensity and pain relief were assessed by patients for each treated BTcP episode during the double-blind efficacy phase.
 - Pain intensity was measured using an 11-point scale where 0 was 'no pain' and 10 was 'pain as bad as you can imagine'.
 - Pain relief was measured using a 5-point scale, where 0 was 'no relief' and 4 was 'complete relief'.
 - Assessments were made immediately before SLF administration (pain intensity) and at 10, 15, 30 and 60 minutes thereafter (pain intensity and pain relief).
- The primary efficacy variable was the sum of pain intensity differences (SPID) from baseline over 30 minutes post-dose.
- Secondary efficacy variables included SPID over 60 minutes, pain intensity differences (PID) and pain relief scores at each post-dose time point and the use of rescue medication.
- Adverse events were recorded throughout both studies.

Results

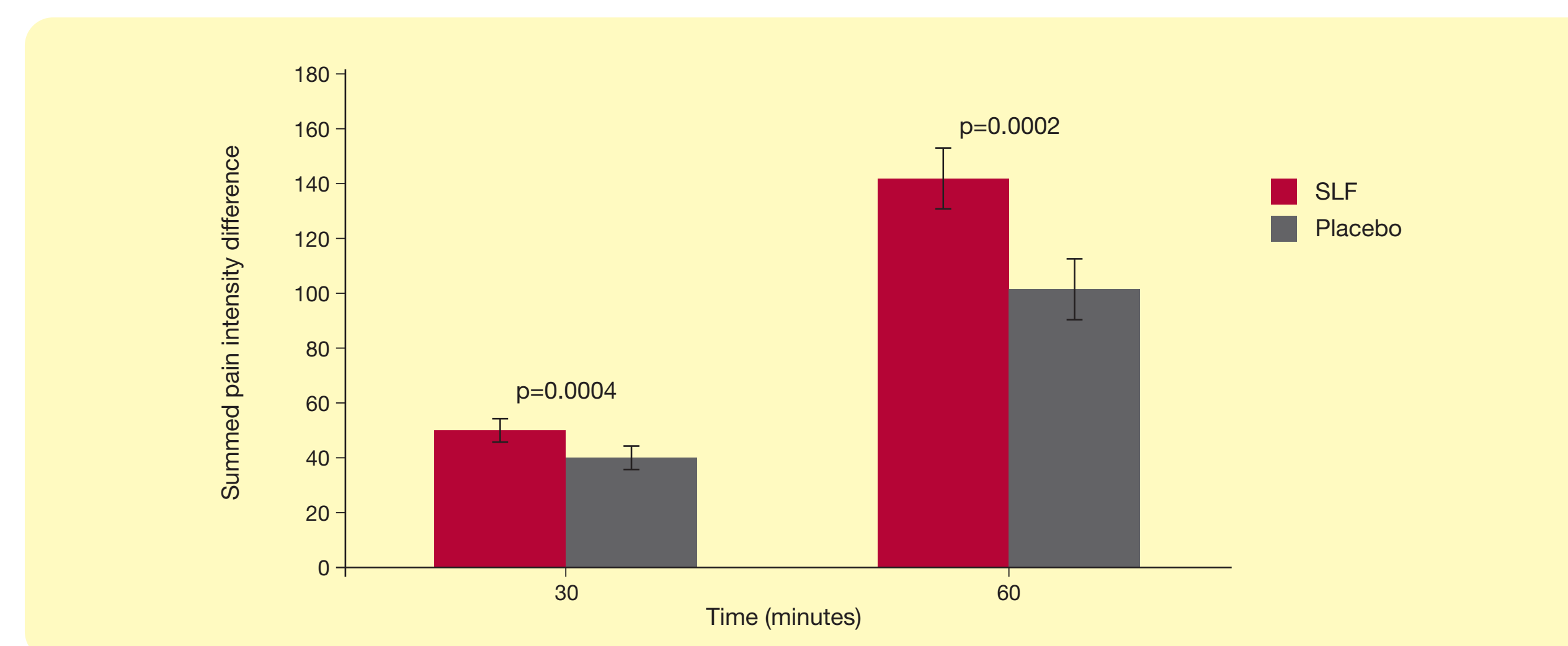
Interim analyses

- While the studies were ongoing, interim analyses of the efficacy and safety data were performed in September 2007 and January 2008, respectively.
- At the second interim analysis, a total of 219 patients were enrolled:
 - 131 successfully completed the titration phase
 - 61 entered the efficacy phase (study 005 only; ITT population)
 - 70 completed the 3-month follow-up and 28 completed the 12 month follow-up.

Efficacy assessments (study 005)

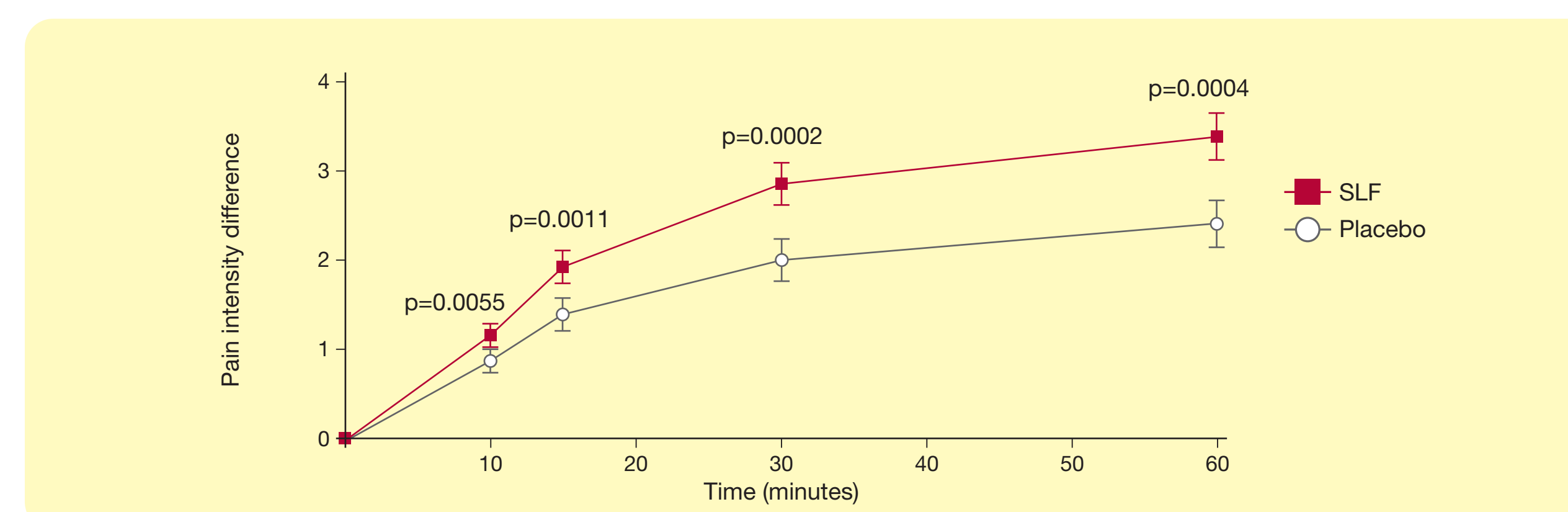
- The mean SPID at 30 minutes post-dose was significantly greater with SLF than with placebo ($p=0.0004$; Figure 2).
- The improvement in SPID compared to placebo was maintained to 60 minutes post dose ($p=0.0002$; Figure 2).

Figure 2. Mean summed pain intensity difference from baseline to 30 and 60 minutes post-administration for sublingual fentanyl citrate and placebo (ITT population, $n=61$). SLF, sublingual fentanyl citrate



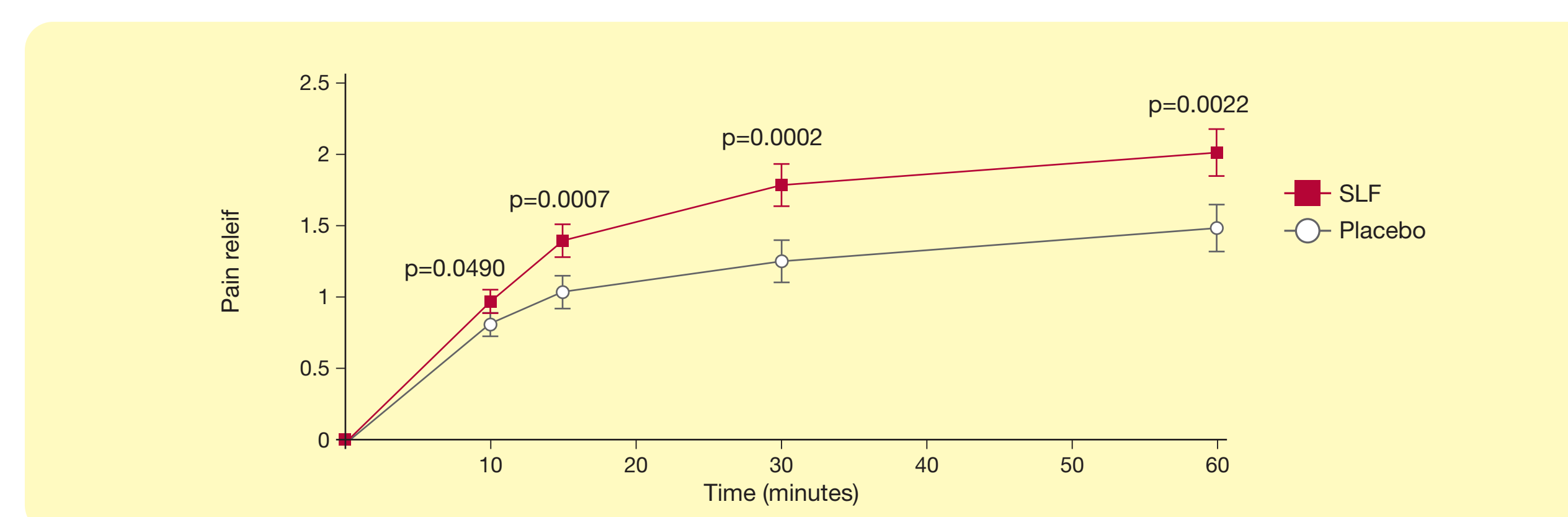
- Treatment of BTcP episodes with SLF demonstrated a significantly improved PID relative to placebo from as early as 10 minutes post-dose ($p=0.0055$; Figure 3).
- The significant improvements in PID with SLF compared to placebo were maintained over the 60-minute assessment period ($p\leq 0.0055$; Figure 3).

Figure 3. Pain intensity difference from baseline with sublingual fentanyl citrate and placebo (ITT population, $n=61$). SLF, sublingual fentanyl citrate



- SLF provided significantly greater pain relief compared to placebo from as early as 10 minutes post dose ($p\leq 0.049$) and throughout the 60-minute assessment period (Figure 4).

Figure 4. Pain relief with sublingual fentanyl citrate and placebo (ITT population, $n=61$). SLF, sublingual fentanyl citrate



- Of the BTcP episodes treated with study medication, 11.2% of those treated with SLF required use of rescue medication by the patient compared to 27.2% of those treated with placebo.

Safety and tolerability

- At interim analysis, the incidence of serious adverse events (SAEs) was assessed in a total of 219 patients (more detailed safety data were not available at the interim assessment).
- 55 patients experienced a total of 106 SAEs.
- No SAEs were deemed to be related to study medication, but were related to the underlying disease states and physical conditions of the patients.

Conclusions

- SLF was associated with significantly greater improvements in pain intensity and pain relief compared to placebo, from as early as 10 minutes post-dose.
- Significant improvements in pain intensity over placebo were maintained throughout the 60-minute assessment period.
- Fewer of the BTcP episodes treated with SLF required use of rescue medication by the patient compared to placebo-treated episodes.
- Interim safety data suggest that SLF was well tolerated, with SAEs reflecting the underlying disease state and physical condition of the patients.

References

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