Buprenorphine Buccal Film for Chronic Low Back Pain in 2 Double-blind, Placebo-controlled, Randomized Withdrawal Trials: A Pooled Analysis of Subgroups Based on Baseline Pain Severity

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Introduction

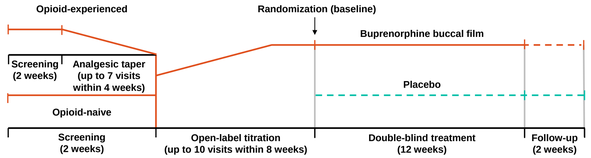
Buprenorphine Buccal Film (BELBUCA®)

- Buprenorphine is an atypical opioid and a partial μ-opioid receptor agonist, with demonstrated efficacy as an analgesic and favorable safety properties that may provide an improved risk-benefit profile relative to other opioids[1]
- As with all Schedule II long-acting opioids, buprenorphine buccal film (BBF) is approved by the US Food and Drug Administration for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate[2]
- Two previous phase 3 clinical trials established the efficacy of BBF for treating chronic low back pain in opioid-naive[3] and opioid-experienced[4] subjects (ClinicalTrials.gov NCT01633944 and NCT01675167, respectively)
- Both studies used an enriched enrollment, randomized withdrawal design that consisted of an open-label BBF titration phase followed by a randomized, double-blind phase in which subjects either continued treatment with BBF or were switched to placebo[3,4] (**Figure 1**)
- After 12 weeks of double-blind treatment, mean average daily pain scores worsened significantly less from baseline in subjects who continued use of BBF than in those who switched to placebo[3,4]
- Subjects in the BBF group also had significantly lower pain scores at Week 1 and at all subsequent time points through Week 12[3,4]

Objective

- This post hoc analysis pooled data from both aforementioned clinical trials to characterize further the efficacy of BBF on the basis of baseline pain severity

Figure 1. Study Design of 2 Primary, Enriched Enrollment, Randomized Withdrawal Trials[3,4]



Methods

Subjects

- Both studies enrolled adults aged ≥18 years who had chronic low back pain for ≥6 months as their primary source of pain
- To enter the open-label titration phase, subjects had to have an average pain intensity score of ≥5 on an 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) during the last week of screening
- Opioid-experienced subjects with well-controlled pain (average pain intensity <5) were also permitted to enroll, provided that their pain scores were at ≥5 for at least 3 consecutive days during taper of their previous opioid

Primary Study Procedures

- After titration to their optimal BBF dose during the open-label phase, eligible subjects were randomly assigned (1:1 ratio) to receive continued BBF or placebo buccal film every 12 hours for 12 weeks
- Subjects assigned to receive BBF continued the same optimal dose reached at the end of the open-label titration phase

Methods (cont'd)

Primary Study Procedures (cont'd)

- Rescue medication was provided to minimize the risk of opioid withdrawal in subjects randomized to placebo
  - Opioid-experienced and opioid-naïve subjects were permitted 1 or 2 tablets of hydrocodone/acetaminophen (HC/APAP 5/325 mg) for up to 2 doses each day during the first 2 weeks; opioid-experienced subjects were allowed 1 dose of HC/APAP per day thereafter, while opioid-naïve subjects were provided APAP 500 mg thereafter

Post Hoc Analyses

- Post hoc analyses combined data for subjects from both studies and evaluated the mean difference in average daily NRS scores from baseline (the start of double-blind treatment) in 10-day intervals through Day 80
- Subjects were stratified by average pain severity in the 7 days before the start of open-label titration, with mild pain defined as an average NRS of ≤4, moderate pain as an average NRS of 5 or 6, and severe pain as an average NRS ≥7

Results

Demographics and Baseline Characteristics

- Across both studies, 971 subjects were randomly assigned to BBF or placebo (**Table 1**)
- Mean (SD) NRS pain scores before open-label titration were similar in both treatment groups at the start of the double-blind period (**Table 1**)

Table 1. Baseline Characteristics at the Start of the Double-blind Phase

Characteristic	Overall		Pain Prior to Titration					
			Mild (NRS 0-4)		Moderate (NRS 5-6)		Severe (NRS 7-10)	
	BBF	Placebo	BBF	Placebo	BBF	Placebo	BBF	Placebo
n	483	488	15	23	102	94	366	371
Age, mean (SD), y	52.0 (11.8)	51.9 (12.4)	53.3 (12.0)	58.4 (12.3)	53.9 (11.7)	55.6 (12.2)	51.4 (11.8)	50.5 (12.1)
Sex, no. (%)								
Female	260 (54)	278 (57)	10 (67)	11 (48)	48 (47)	48 (51)	202 (55)	219 (59)
Male	223 (46)	210 (43)	5 (33)	12 (52)	54 (53)	46 (49)	164 (45)	152 (41)
Race, no. (%)								
American Indian or Alaska Native	0	4 (1)	0	0	0	0	0	4 (1)
Asian	9 (2)	22 (5)	1 (7)	0	1 (1)	6 (6)	7 (2)	16 (4)
Black or African American	104 (22)	108 (22)	3 (20)	2 (9)	11 (11)	11 (12)	90 (25)	95 (26)
White	369 (76)	351 (72)	11 (73)	21 (91)	89 (87)	77 (82)	269 (73)	253 (68)
Other	1 (<1)	2 (<1)	0	0	1 (1)	0	0	2 (1)
Average NRS pain score prior to titration, mean (SD)	7.0 (1.2)	6.9 (1.2)	4.2 (0.6)	4.3 (0.6)	5.6 (0.4)	5.5 (0.3)	7.5 (0.8)	7.5 (0.8)
Average NRS pain score prior to randomization, mean (SD)	2.9 (1.0)	2.8 (1.1)	2.7 (1.1)	2.3 (0.8)	2.6 (0.9)	2.7 (0.8)	3.0 (1.0)	2.9 (1.1)

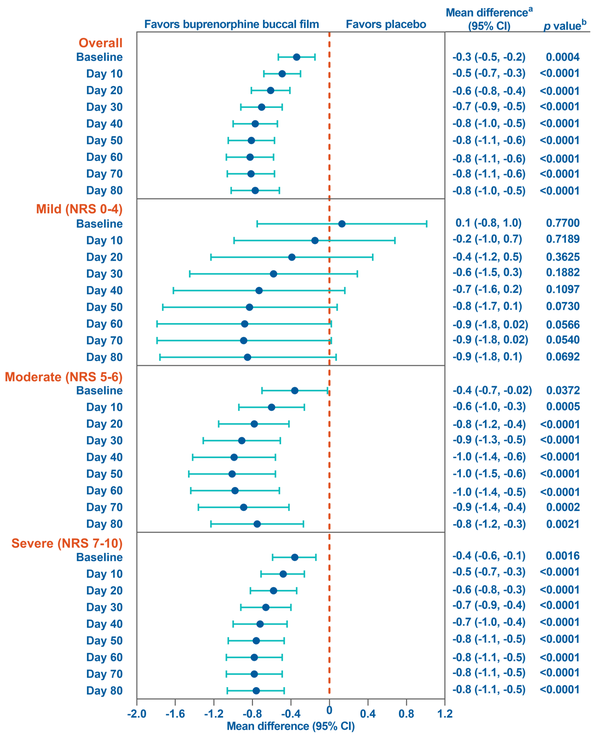
Abbreviations: BBF, buprenorphine buccal film; NRS, numerical rating scale; SD, standard deviation.

Mean Differences in NRS Pain Scores

- Overall, improvements in pain scores were significantly greater for the BBF group than for the placebo group in every 10-day interval assessed (**Figure 2**)

Results (cont'd)

Figure 2. Mean NRS Pain Score Differences Between BBF and Placebo During the Double-blind Phase, Stratified by Pain Severity Subgroups Using NRS Pain Scores Prior to Titration



[a]A linear mixed-effects model was used to assess differences between the groups in individual NRS pain scores. The mean pain score over time adjusted for baseline was used to assess the change in pain intensity scores from baseline to Week 12. Estimates of mean treatment differences were calculated using a quadratic model that provided a conservative estimate of the difference as the model was adjusted to fit excess differential dropouts over time in the placebo arm. [b]The *p* values were calculated using the least squares means at each time point from the quadratic model.
Abbreviations: CI, confidence interval; NRS, numerical rating scale.

Results (cont'd)

Mean Differences in NRS Pain Scores (cont'd)

- For subjects with moderate or severe pain, the BBF group had significantly greater decreases in pain scores than the placebo group at every 10-day interval assessed; the same was not observed for subjects with mild pain
- Mean differences in pain scores between the BBF and placebo groups were greatest at Day 50 in the moderate pain subgroup and at Day 60 and Day 70 in the severe pain subgroup
- Mean differences in pain scores between the BBF group and placebo groups were similar for subjects in the moderate and severe pain subgroups at every 10-day interval assessed

Conclusions

- **BBF has demonstrated analgesic efficacy for the treatment of chronic low back pain in opioid-naive and opioid-experienced patients**
- **The results of this post hoc analysis indicate that treatment with BBF results in a greater reduction in pain than does placebo; overall pooled efficacy results were driven mainly by improvements in subjects with moderate or severe pain at baseline; similar reductions in pain were observed regardless of whether subjects had moderate or severe pain at study entry**
  - **A lack of significant differences in subjects with mild pain may be attributable to the large variance, the small number of subjects with mild pain at baseline, and/or floor effects on efficacy**
- **Given the favorable risk-benefit profile of buprenorphine, BBF should be considered a treatment option for patients who require long-term opioid treatment, even when their pain levels are considered severe**

References

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Author Disclosures

- **CM** is a former employee of BioDelivery Sciences International, Inc. **GC** has received compensation for participation in data and safety monitoring boards from AstraZeneca, AveXis, BioLineRx, BrainStorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Horizon Therapeutics, Hisun Pharmaceuticals, Mapi Pharma, Merck, Merck/Pfizer, OPKO Biologics, OncoImmune, Neurim, Novartis, Orphazyme, Sanofi, Reata Pharmaceuticals, Teva Pharmaceuticals, Viela Bio, and Vivus; for participation in a protocol review committee for the National Heart, Lung, and Blood Institute; for participation in an obstetric-fetal pharmacology research unit oversight committee for the National Institute of Child Health and Human Development; and for participation in consulting or advisory boards for BioDelivery Sciences International, Inc., Biogen, Click Therapeutics, Sanofi Genzyme, Genentech, GW Pharmaceuticals, Klein Buendel, MedImmune, MedDay, Neurogenesis, Novartis, Osmotica Pharmaceuticals, Perception Neuroscience, Recursion Pharma/CereXis, Roche, and TG Therapeutics. **PHA** declares no conflicts of interest.

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