Evaluation of the Tolerability of Switching Patients on Chronic Full Opioid Agonist Therapy to Buprenorphine HCl Buccal Film

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INTRODUCTION

- Buprenorphine is a partial mu-agonist with poor oral bioavailability, requiring transmucosal, transdermal or parenteral administration for analgesia.
- Buprenorphine HCl buccal film is a transmucosal form of buprenorphine, utilizing BioErodible MucoAdhesive (BEMA®) delivery technology. This buccal buprenorphine formulation (BBup) is currently being investigated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[1,2]
- Due to its partial agonist activity and high affinity for mu-opioid receptors, there is a potential for buprenorphine to precipitate withdrawal in patients who are already on full mu-opioid agonists. Accordingly, current practice is to taper a patient's around-the-clock (ATC) opioid to a 30 mg morphine sulfate equivalent (MSE) dose before switching to buprenorphine.[3]

OBJECTIVE

To determine whether patients with chronic pain receiving 80 to 220 mg oral morphine sulfate equivalent (MSE) of an around-the-clock (ATC) full mu-opioid agonist could be safely transitioned to buprenorphine HCl buccal film (BBup) at approximately 50% of their oral MSE dose without inducing opioid withdrawal or sacrificing analgesic efficacy.

METHODS

Study Design

- Randomized, double-blind, double-dummy, active-controlled, 2-period crossover study.
- Male or female patients 18–60 years of age receiving ATC full mu-opioid agonist therapy of either morphine sulfate or oxycodone HCl and
  - with ≥6–month history of chronic pain (including peripheral neuropathic pain)
  - requiring ATC opioid therapy with 80–220 mg MSE per day ATC for ≥28 days
  - confirmed to be opioid dependent by naloxone challenge
- Patients entered a 7– to 14–day screening period, during which they continued to receive their full mu-opioid agonist therapy ATC.
- Visit 1 (screening): Patients assessed for protocol eligibility, including the naloxone challenge.
- Visit 2: Eligible patients returned to the clinic 7 to 14 days later and were admitted for 2 consecutive nights.
  - Patients randomized to 1 of 2 treatment sequences, AB or BA.
    - Treatment A: 2 doses of buprenorphine HCl buccal film (either 300 or 450 µg).
    - Treatment B: 2 doses of full mu-agonist active ATC opioid (50% of original MSE dose).
  - Study drug administered as identically appearing buccal film containing either buprenorphine or placebo plus overencapsulated tablets containing morphine (IR or ER), oxycodone (IR or ER), or matching placebo (double-blind, double-dummy).
  - Patients were administered the first dose of study drug treatment according to their randomized sequence and monitored in the clinic for signs and symptoms of opioid withdrawal for 12 hours, at which time a second dose of study drug was administered with an additional 12-hour monitoring period.
  - On Day 3, 24 hours after the first dose of study drug, the subjects received their usual dose of ATC opioid and remained in the clinic for approximately 12 hours to ensure that transition back to the original analgesic regimen was adequate for pain control before being discharged to continue outpatient treatment.
- Visit 3: Patients returned to the clinic 7 to 14 days later, where they underwent the same procedures but received the alternate treatment.
- Buprenorphine dose was based on a 100:1 conversion ratio from morphine to buprenorphine to minimize the risk of overdosing by underestimating the potency of buprenorphine. BBup 300-µg and 450-µg doses were selected because they represent relative equivalence to 50% of the patients' MSE.
- Randomized patients were stratified into 2 groups based on their original ATC MSE dose at a ratio of 2:1.
  - MSE dose group 1 was composed of patients requiring between 80-160 mg MSE per day.
  - MSE dose group 2 was composed of patients requiring between 161-220 mg MSE per day. Because of slow enrollment in the higher dose group, the study was closed with only the 80- to 160-mg MSE group fully enrolled.
- During the 24-hour period following the initial study dose, no analgesics were administered with the exception of ibuprofen 400 to 600 mg PRN to treat pain, if necessary.
- **Table 1** outlines the range of original MSE doses, examples of opioid study dose calculations, and BBup study dose assignments.

Table 1. Original MSE Doses and Study Dose Calculations/Assignments

Original MSE Total Daily Dose,* mg	Original MSE Q12h Dose,† mg (Total Daily Dose ÷ 2)	MSE Study Dose‡ Q12h, mg	BBup Study Dose§ Q12h	Study Group
80–160	40–80	20–40	0.3 mg = 300 µg	1
161–220	81–110	41–55	0.45 mg = 450 µg	2

BBup = buprenorphine HCl buccal film; MSE=morphine sulfate equivalent; Q12h=every 12 hours.
*If starting with oxycodone, assumes oxycodone to morphine ratio of 2:3.
†MSE total daily dose divided into 2 Q12h doses.
‡Fifty percent of the total daily dose, administered Q12h.
§Assumes buprenorphine to morphine analgesic ratio of 100:1.

Assessments

Opioid Withdrawal Assessments

- Clinical Opioid Withdrawal Scale (COWS) - Measures 11 opioid withdrawal signs and symptoms in physically dependent patients, including pulse rate, sweating, restlessness, pupil size, bone/joint aches, runny nose or tearing, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin.
  - Each item is scored from 0 to 4 or 5 for a COWS total score of 0 to 48; the greater the score, the more severe the withdrawal.
    - 0-4 = no withdrawal, 5-12 = mild, 13-24 = moderate, 25-36 = moderately severe, >36 = severe withdrawal
  - The COWS was administered:
    - 0.5 hours before each dose of study medication;
    - 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, and 12 hours after the first dose; and
    - 0.5, 1, 1.5, 2, 4, and 12 hours after the second dose of study drug during each period.

Pain Assessments

- During periods 1 and 2, patients rated their "Pain Now" intensity on a 0-10 numerical rating scale (NRS) [0 - "No pain"; 10 - "Pain as bad as you can imagine "]
  - 0.5 hours before each dose of study medication;
  - 0.5, 1, 2, 4, 9, and 12 hours after the first dose; and
  - 0.5, 1, 2, 4, and 12 hours after the second dose.

Safety Assessments

- Safety evaluations included Adverse Events (AE), laboratory and electrocardiogram findings, and suicidality as measured by the Columbia-Suicide Severity Rating (C-SSRS).

Statistical Analyses

- Safety population - all patients who received at least 1 dose of study treatment.
- Per-protocol (PP) population - all patients from the safety population who were randomized and did not have major protocol deviations that may have confounded interpretation of the COWS, who completed both crossover periods, and who provided at least the first 4 hours of COWS data for each of the 2 treatment periods.
- The primary endpoint was significant opioid withdrawal symptoms defined as a COWS score ≥13 or requirement for rescue because of withdrawal symptoms. The rate of significant withdrawal in each treatment group was estimated using a logistic regression model with repeated measures.
- Numerical rating scale pain score was analyzed in the same manner as COWS total score; NRS pain score obtained at –0.5 hours for a treatment was defined as the baseline value for that treatment.
- The number and percentage of patients reporting treatment-emergent AEs in each treatment group was tabulated by treatment group, system organ class and preferred term, severity, and relationship to study medication. All AEs were attributed to 1 of the study treatments based on the onset time of the events.

RESULTS

Study Patients

Disposition

- Thirty-nine patients were randomized (Safety Population):
  - 33 to MSE dose group 1 (80–160 mg).
    - 31 (93.9%) completed both periods of the study.
    - 1 discontinued BBup because of an AE.
    - 1 discontinued full mu-opioid agonist treatment due to lost to follow-up.
  - 6 to MSE dose group 2 (161–220 mg).
    - 5 (83.3%) completed the study.
    - One patient discontinued after the first treatment period (BBup) and was lost to follow-up.

Demographic and Baseline Characteristics

- Demographic and baseline characteristics are shown in **Table 2**.
- The median age was 43, and the majority of patients were white (74%) and obese, with a slight majority female.

Table 2. Patient Demographics and Baseline Characteristics (Safety Population)

	MSE Dose Group 1 n=33	MSE Dose Group 2 n=6	Overall n=39
Age, y			
Mean ± SD	41.6 (8.91)	46.0 (10.33)	42.3 (9.13)
Median	43	44	43.0
Range	26–55	31–60	26–60
Sex, n (%)			
Male	16 (48.5)	2 (33.3)	18 (46.2)
Female	17 (51.5)	4 (66.7)	21 (53.8)
Race, n (%)			
White	24 (72.7)	5 (83.3)	29 (74.4)
Black or African American	9 (27.3)	0	9 (23.1)
American Indian or Alaska native	0	1 (16.7)	1 (2.6)
Ethnicity, n (%)			
Hispanic	3 (9.1)	0	3 (7.7)
Non-Hispanic	30 (90.9)	6 (100)	36 (92.3)
Weight, kg			
Mean ± SD	95.0 (23.84)	76.8 (20.11)	92.2 (24.00)
Median	92.1	78.1	87.5
Range	40–142	53–108	40–142
Height, cm			
Mean ± SD	169.5 (9.05)	168.9 (10.01)	169.4 (9.07)
Median	167.6	166.2	167.6
Range	150–185	158–185	150–185
Body mass index, kg/m2			
Mean ± SD	33.0 (7.91)	26.9 (7.03)	32.1 (8.01)
Median	33.7	25.9	33.0
Range	15–50	19–40	15–50

Withdrawal Analysis

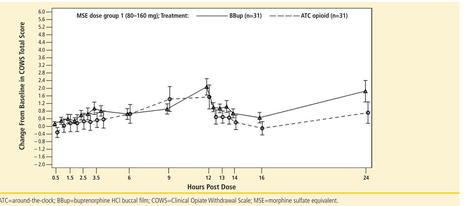
- For the PP Population, 35 subjects (31 on 80–160 mg and 4 on 161–220 mg oral MSE/day) completed both periods of the study and were evaluable for opioid withdrawal status.
  - Of these 35 subjects, significant withdrawal was experienced by 1 subject on buccal buprenorphine and 2 subjects on the full agonist.
  - No subject had a COWS total score of ≥13 up to 6 hours post dose in the PP Population, indicating no difference between buprenorphine and ATC opioid in the risk of precipitated withdrawal.
  - Only 2 patients in MSE dose group 1 met the significant withdrawal definition.
    - 1 experienced withdrawal with both study drug treatments and the second with full mu-opioid agonist only.
  - None of the 6 patients in MSE dose group 2 met the significant withdrawal definition.
- The maximum COWS total score or change in maximum COWS score from baseline was similar in the 2 MSE dose groups.
  - As shown in **Table 3**, mean maximum COWS scores were similar between buccal buprenorphine and full mu-opioid agonist treatments (mean [SD] 4.6 [3.15] and 5.3 [4.42], respectively.
  - Mean change from baseline in COWS total score during the 24-hour study periods was similar for both treatment groups for MSE dose group 1, as depicted in **Figure 1.**
  - COWS scores were low during the 4 to 6 hours post dose and increased slightly by the end of each 12-hour dosing period. The percent of subjects in each withdrawal severity category across the observation period is shown in **Figure 2**.

Table 3. Comparison of Maximum COWS Total Score (Per-Protocol Population)

MSE Dose Group	Statistic	BBup	ATC Opioid*	P Value†
Group 1 80–160 mg	n	31	31	0.7942
	Mean (SD)	4.6 (3.15)	5.3 (4.42)	
Group 2 161–220 mg	n	4	4	0.6155
	Mean (SD)	5.5 (1.91)	6.3 (2.50)	

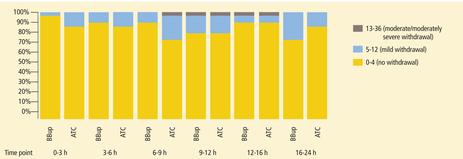
ATC=around-the-clock; BBup=buprenorphine HCl buccal film; COWS=Clinical Opiate Withdrawal Scale; MSE=morphine sulfate equivalent.
*ATC opioid: morphine sulfate or oxycodone.
†P Values were generated using a linear mixed model including sequence, period, and treatment as fixed effects, patient within sequence as random effect, and baseline COWS total score as a covariate.

Figure 1. Mean (± SE) change from baseline of COWS at selected time points (80– to 160–mg MSE cohort, per-protocol population).



ATC=around-the-clock; BBup=buprenorphine HCl buccal film; COWS=Clinical Opiate Withdrawal Scale; MSE=morphine sulfate equivalent.

Figure 2. Percent of patients with each COWS category at selected time points (80- to 160-mg MSE cohort, per-protocol population).

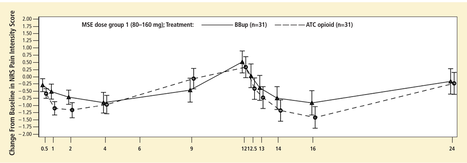


ATC=around-the-clock; BBup=buprenorphine HCl buccal film; COWS=Clinical Opiate Withdrawal Scale; MSE=morphine sulfate equivalent.

Pain Scores

- There were no between treatment differences in changes from baseline in NRS pain scores over the 24-hour study periods for MSE dose group 1 (80–160 mg MSE) **(Figure 3)**. The sample size for MSE dose group 2 (161–220 mg MSE) was too small to analyze.

Figure 3. Mean (± SE) change from baseline of NRS pain intensity score at selected time points (80– to 160–mg MSE cohort, per-protocol population)



ATC=around-the-clock; BBup=buprenorphine HCl buccal film; MSE=morphine sulfate equivalent; NRS=numerical rating scale.

Safety

- Adverse events are summarized in **Table 4**.
- Overall, AEs were reported in 20 patients (60.6%) in MSE dose group 1 and in 1 patient (16.7%) in MSE dose group 2
- In MSE dose group 1, 18 patients (56.3%) had at least 1 AE during BBup treatment, and 13 patients (40.6%) had at least 1 AE during full mu-opioid agonist therapy.
  - Discontinuations due to AEs occurred with 1 patient during treatment with BBup and 3 patients during full mu-opioid agonist treatment.
  - The most frequent AEs with BBup were headache (18.8%); vomiting (12.5%); and nausea, diarrhea, and drug withdrawal syndrome (each 9.4%). The most frequent AEs with full opioid agonist were headache (15.6%); drug withdrawal syndrome (12.5%); and nausea (6.3%).
- In MSE dose group 2, one patient experienced drug withdrawal syndrome during BBup treatment, which led to discontinuation.
- Drug withdrawal syndrome was reported in 3 patients during BBup treatment and 4 patients during full mu-opioid agonist treatment in MSE dose group 1, and 1 patient during BBup treatment in MSE dose group 2.
- No deaths occurred during the study; 1 patient in MSE dose group 1 experienced serious AEs of chest pain and dyspnea, which were considered unlikely related to either buprenorphine or ATC opioid therapy.
- No clinically meaningful trends were noted in laboratory test results, vital signs, physical examination findings, or C-SSRS.

Table 4. Number (%) of Patients With TEAEs – Safety Population

System Organ Class Preferred Term, n (%)	MSE Dose Group 1 (80–160 mg)			MSE Dose Group 2 (161–220 mg)		
	BBup n=32	ATC Opioid* n=32	Overall n=33	BBup n=6	ATC Opioid* n=5	Overall n=6
Number of subjects with at least 1 treatment-emergent adverse event	18 (56.3)	13 (40.6)	20 (60.6)	1 (16.7)	0	1 (16.7)
Gastrointestinal disorders	7 (21.9)	5 (15.6)	10 (30.3)	0	0	0
Nausea	3 (9.4)	2 (6.3)	5 (15.2)	0	0	0
Diarrhea	3 (9.4)	1 (3.1)	4 (12.1)	0	0	0
Vomiting	4 (12.5)	1 (3.1)	4 (12.1)	0	0	0
Abdominal discomfort	0	1 (3.1)	1 (3.1)	0	0	0
General disorders and administration site conditions	4 (12.5)	4 (12.5)	6 (18.2)	1 (16.7)	0	1 (16.7)
Drug withdrawal syndrome	3 (9.4)	4 (12.5)	5 (15.2)	1 (16.7)	0	1 (16.7)
Chest pain	1 (3.1)	0	1 (3.0)	0	0	0
Investigations	1 (3.1)	0	1 (3.0)	0	0	0
Oxygen saturation decreased	1 (3.1)	0	1 (3.0)	0	0	0
Musculoskeletal and connective tissue disorders	2 (6.3)	0	2 (6.1)	0	0	0
Arthralgia	1 (3.1)	0	1 (3.0)	0	0	0
Back pain	1 (3.1)	0	1 (3.0)	0	0	0
Nervous system disorders	8 (25.0)	5 (15.6)	11 (33.3)	0	0	0
Headache	6 (18.8)	5 (15.6)	9 (27.3)	0	0	0
Dizziness	1 (3.1)	0	1 (3.0)	0	0	0
Somnolence	1 (3.1)	0	1 (3.0)	0	0	0
Respiratory, thoracic, and mediastinal disorders	1 (3.1)	1 (3.1)	2 (6.1)	0	0	0
Dyspnea	1 (3.1)	0	1 (3.1)	0	0	0
Hypoxia	0	1 (3.1)	1 (3.1)	0	0	0

ATC=around-the-clock; BBup=buprenorphine HCl buccal film; TEAE=treatment-emergent adverse event. *ATC opioid = morphine sulfate or oxycodone.
At each level of patient summarization, a patient is counted once if the patient reported 1 or more events (n).

CONCLUSION

- The results demonstrate that in this study, chronic pain patients treated with around-the-clock full mu-opioid agonist therapy in the dose range of 80–220 mg MSE were successfully switched to buprenorphine HCl buccal film (partial mu-opioid agonist), without the need for an opioid taper, at approximately 50% of the full mu-opioid agonist dose without an increased risk of experiencing opioid withdrawal.
- There were no treatment differences in pain scores in the 80–160 mg MSE dose range.
- In these opioid-dependent chronic pain patients receiving ATC full mu-opioid agonist doses of 80–220 mg MSE, administration of 300 or 450 µg doses of buprenorphine HCl buccal film 8–12 hours after the last full mu-opioid agonist dose was not associated with a higher incidence of opioid withdrawal or adverse events compared to the 50% ATC full mu-opioid agonist dose.

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