

Evaluation of the Tolerability of Switching Patients on Chronic Full μ -Opioid Agonist Therapy to Buccal Buprenorphine

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Abstract

Objective Assess whether patients with chronic pain receiving 80 to 220 mg oral morphine sulfate equivalent of a full μ -opioid agonist could be transitioned to buccal buprenorphine at approximately 50% of their full dose without inducing opioid withdrawal or sacrificing analgesic efficacy.

Methods. A randomized, double-blind, double-dummy, active-controlled, two-period crossover study in adult patients receiving around-the-clock full opioid agonist therapy and confirmed to be opioid dependent by naloxone challenge. Study doses were substituted at the time of the regular dose schedule for each patient. The primary endpoint was the proportion of patients with a maximum Clinical Opiate Withdrawal Scale score ≥ 13 (moderate withdrawal) or use of rescue medication.

Results. 35 subjects on ≥ 80 mg morphine sulfate equivalent per day were evaluable for opioid withdrawal. One patient during buccal buprenorphine treatment and two during 50% full μ -opioid agonist treatment experienced opioid withdrawal of at least moderate intensity. The mean maximum Clinical Opiate Withdrawal Scale scores were similar, and numerically lower on buccal buprenorphine. There were no significant differences in pain ratings between treatments. The most frequent adverse events with buccal buprenorphine were headache (19%), vomiting (13%), nausea, diarrhea, and drug withdrawal syndrome (each 9%), and with full μ -opioid agonist were headache (16%), drug withdrawal syndrome (13%), and nausea (6%).

Conclusions. Chronic pain patients treated with around-the-clock full μ -opioid agonist therapy can be switched to buccal buprenorphine (a partial μ -opioid agonist) at approximately 50% of the full μ -opioid agonist dose without an increased risk of opioid withdrawal or loss of pain control.

Key Words. Buprenorphine Buccal Film; Opioid; Chronic Pain

Introduction

Buprenorphine is a synthetic opioid classified as a Schedule III controlled substance in the United States. Buprenorphine is a partial agonist at the μ -opioid receptor and an antagonist at the κ receptor; it is used for

treating acute and chronic moderate to severe pain as well as opioid dependence [1–5]. It has properties that may provide an improved risk-benefit profile relative to other opioids [6,7], including analgesic efficacy with no reported ceiling and an analgesic potency that has been reported to be 30 to 115 times greater than that of oral morphine sulfate [5,7–10]. Buprenorphine has also been shown to possess a lower potential for adverse events (AEs) commonly associated with opioid use, such as constipation [11–13] and respiratory depression [4,14,15]. Buprenorphine is an agonist at the opioid receptor-like 1 receptor, the activation of which blocks analgesic tolerance and dampens the rewarding effects of opioids [3–5,16,17], presumably lending to buprenorphine's lower potential for abuse and diversion.

A buprenorphine buccal film has been developed using BioErodible MucoAdhesive (BEMA[®]) delivery technology composed of flexible, water-soluble polymeric films that adhere to the moist buccal mucosa and erode [18]. Buccal buprenorphine (BBUP) doses up to 900 µg twice daily have demonstrated efficacy in controlling chronic low back pain in both opioid-naïve and opioid-experienced patients, including those requiring up to 160 mg morphine sulfate equivalent (MSE) per day, with low incidences of AEs typically associated with opioid administration [19,20].

Because buprenorphine has high affinity binding, slow receptor dissociation, and low intrinsic activity at the µ-opioid receptor, administration of buprenorphine to patients with a significant proportion of µ-opioid receptors occupied by a full µ-agonist may result in displacement of the full agonist [21] and induce opioid withdrawal. The present study was designed to determine whether opioid-experienced patients with chronic pain receiving 80 to 220 mg oral MSE daily dose (the dose range commonly used in treating opioid-experienced patients with an around-the-clock [ATC] opioid) could be safely converted to buccal buprenorphine HCl without inducing opioid withdrawal or sacrificing analgesic efficacy.

Current recommendations for switching to the transdermal formulation of buprenorphine available for treating chronic pain call for tapering to the lowest possible dose of a full µ-opioid agonist before switching to buprenorphine and titrating to effect [22]. For patients on higher MSE doses, this approach may necessitate a long taper period that may be more difficult to achieve and may require more clinical oversight than converting to another full agonist at 50% MSE dose. Here we report the results of a double-blind, randomized, controlled trial demonstrating the feasibility of switching opioid-dependent patients with chronic pain directly to BBUP without a taper.

Methods

Participants

Male or female patients 18 to 60 years of age receiving ATC therapy with a full µ-opioid agonist and confirmed to be opioid dependent by naloxone challenge were

eligible for enrollment. In addition, patients were required to fulfill the following criteria at visits 1, 2, and 3: ≥6-month history of chronic pain (including peripheral neuropathic pain) requiring ≥80 but ≤220 mg MSE per day of either morphine sulfate or oxycodone HCl for ≥28 days; displaying signs and symptoms of withdrawal (i.e., Clinical Opiate Withdrawal Scale [COWS] score ≥5) within 5 minutes following naloxone challenge; stable health, as determined by the principal investigator on the basis of medical history, physical examination, and screening laboratory results; and, if female, not pregnant on the basis of screening serum pregnancy test, and not lactating. Patients taking opioid medication other than morphine sulfate or oxycodone HCl were not enrolled in this trial. Reasons for exclusion were clinically significant pulmonary disease; supine systolic blood pressure >180 or <90 mm Hg or diastolic blood pressure >105 or <50 mm Hg at screening; COWS score >4 before the screening naloxone challenge; aspartate aminotransferase or alanine aminotransferase >3 times the upper limits of normal or serum creatinine >1.9 mg/dL at screening; history of alcohol or substance abuse and/or positive urine drug screen or alcohol breath test at screening; or at significant risk for suicidal behavior based on the Columbia-Suicide Severity Rating Scale (C-SSRS). To be eligible, subjects could not have used monoamine oxidase inhibitors within 14 days of screening or during the study; any medication or nutraceutical or herbal product with cytochrome P450 (CYP) 3A4 inhibition or induction properties within 30 days of screening; class IA antiarrhythmic medications or class III antiarrhythmic medications within 14 days of screening; or α2-agonist antihypertensives (e.g., clonidine), 5-HT3 antagonists (e.g., ondansetron), benzodiazepines, or other medications that were anticipated to confound detection of signs and symptoms of opioid withdrawal.

This study was designed and monitored in accordance with good clinical practice as required by the major regulatory authorities and the Declaration of Helsinki. The study protocol and protocol amendment were reviewed and approved by Copernicus Institutional Review Board, Durham, NC. Written informed consent was obtained by the investigator at the screening visit before any assessments were performed.

Study Design

This was a randomized, double-blind, double-dummy, active-controlled, two-period crossover study. Patients entered a 7- to 14-day screening period, during which they continued to receive their full µ-opioid agonist therapy ATC. At visit 1 (screening), patients signed the informed consent and were assessed for protocol eligibility, including the naloxone challenge.

Eligible patients returned to the clinic 7 to 14 days later and were admitted for two consecutive nights. Patients were randomized to one of two treatment sequences, AB or BA, where treatment A was two doses of BBUP

Table 1 Original MSE doses and study dose calculations/assignments

Original MSE total daily dose,* mg	Original MSE Q12h dose, [†] mg (total daily dose \div 2)	MSE study dose [‡] Q12h, mg	BBUP [§] study dose Q12h	Study group
80 – 160	40 – 80	20 – 40	0.3 mg = 300 μ g	1
161 – 220	81 – 110	41 – 55	0.45 mg = 450 μ g	2

BBUP = Buccal buprenorphine; 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.

and treatment B was two doses of active full μ -opioid agonist. A conversion ratio of 100:1 for morphine to buprenorphine dose was used for this study. A subject's original MSE dose was reduced to 50%, and the subject was given either 300 or 450 μ g of buprenorphine. Table 1 outlines the range of original MSE doses, examples of opioid study dose calculations, and BBUP study dose assignments.

Study drug was administered as identically appearing buccal film containing either buprenorphine or placebo plus overencapsulated tablets containing morphine sulfate (IR or ER), oxycodone (IR or ER), or matching placebo (double-blind, double-dummy). Patients were administered the first dose of study drug 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 patients received their usual dose of full μ -opioid agonist 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.

Patients returned to the clinic 7 to 14 days later to be admitted for visit 3, where they underwent the same procedures but received the alternate treatment.

Buprenorphine dose was based on a 100:1 conversion ratio for morphine to buprenorphine to minimize the risk of overdosing by underestimating the potency of buprenorphine. BBUP 300- μ g and 450- μ g doses were selected because they represent relative equivalence to 50% of the patients' MSE. Randomized patients were stratified into two groups based on their original ATC MSE. MSE Dose Group 1 was composed of patients requiring between 80 and 160 mg MSE per day, and MSE Dose Group 2 was composed of patients requiring between 161 and 220 mg MSE per day for \geq 28 days. Patients were transitioned only from morphine sulfate or oxycodone HCl ATC. Because of slow enrollment in the higher dose group, the study was closed with only the 80- to 160-mg MSE group fully enrolled.

Opioid Withdrawal Assessments

The 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. A score $>$ 13 is consistent with moderate 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 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 using an 11-point numerical rating scale (NRS) from 0 to 10, where 0 represents "No pain" and 10 represents "Pain as bad as you can imagine."

Safety Assessments

Safety evaluations included AEs, laboratory and electrocardiogram findings, and suicidality as measured by the C-SSRS.

Statistical Analysis

Safety analyses were performed on all patients who received at least one dose of study drug.

Other analyses were performed using the per-protocol population, which included 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 two treatment periods.

The primary endpoint was the proportion of patients who experienced opioid withdrawal, defined as a maximum COWS score of ≥ 13 , or required rescue medication because of withdrawal symptoms during the 24-hour study period. The rate of withdrawal in each treatment group was estimated using a logistic regression model with repeated measures. It was assumed that the withdrawal rate difference between BBUP and full μ -opioid agonist was 25%. With 32 patients, the 95% CI for the percentage withdrawal rate difference was 5.6% to 44.3%. The maximum COWS score was based on all available data (i.e., the missing values were not imputed). In addition, COWS total scores at each time point were summarized using descriptive statistics by treatment for each MSE dose group and overall. COWS at each time point and maximum COWS total score were summarized using frequency and percentage based on this rating by treatment group for each MSE dose group and overall.

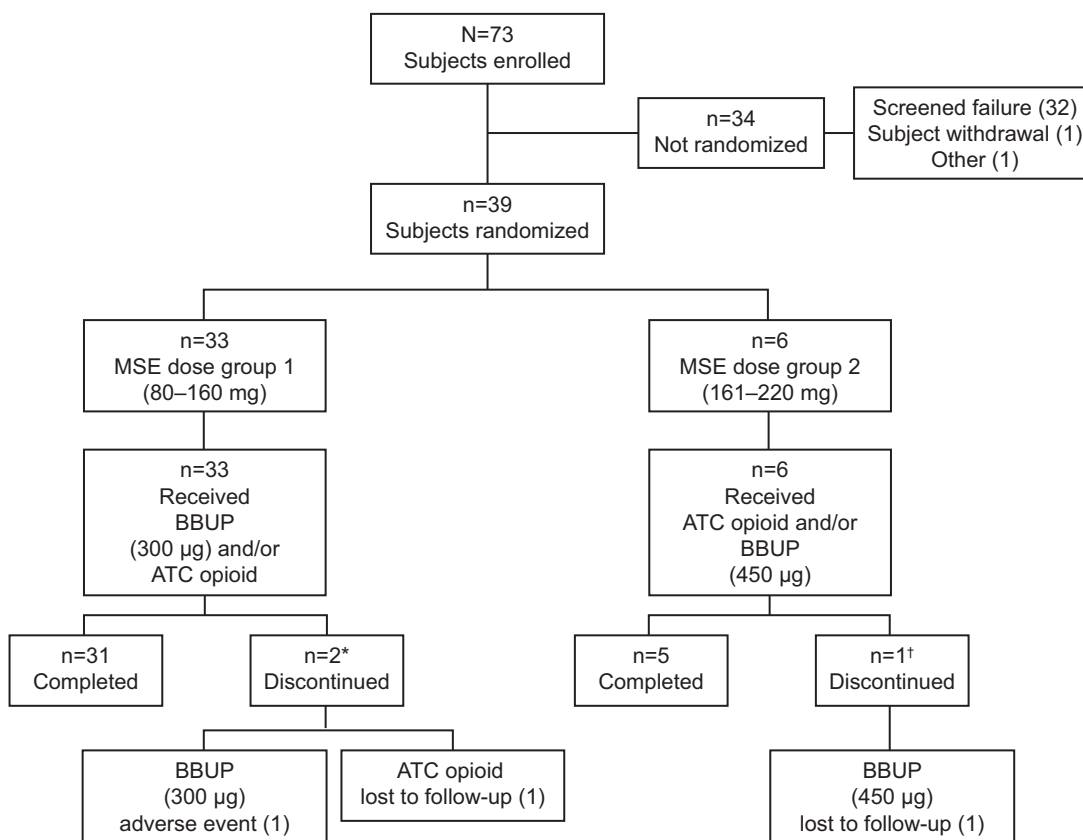
The numerical rating scale pain score was analyzed in the same manner as the COWS total score; NRS pain score obtained at -0.5 hours for a treatment was defined as the baseline value for that treatment.

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 one of the study treatments based on the onset time of the events.

Results

Patient Disposition

Disposition of patients is shown in Figure 1. Thirty-nine patients were randomized, 33 to MSE Dose Group 1 (80–160 mg) and 6 to MSE Dose Group 2



*One subject (MSE Dose Group 1) received buprenorphine 300 µg at visit 2 but did not return for visit 3 to receive full μ -opioid agonist because of a serious adverse event. Another subject (MSE Dose Group 1) received full μ -opioid agonist at visit 2 but did not return for visit 3 to receive buprenorphine.

†One subject (MSE Dose Group 2) received buprenorphine (450 µg) at visit 2 but did not return for visit 3 to receive full μ -opioid agonist.

Figure 1 Patient disposition. ATC = around-the-clock; BBUP = buccal buprenorphine; MSE = morphine sulfate equivalent.

(161 – 220 mg). Among these patients, 43.6% took an IR formulation, 35.9% took an ER formulation, and 20.5% took both types of formulations of full μ -opioid agonist during the double-blind treatment period. When used, the IR product or placebos were administered on a scheduled basis, not as needed.

Table 2 Patient demographics and baseline characteristics (safety population)

	MSE dose group 1 n = 33	MSE dose group 2 n = 6
Age, y		
Mean \pm SD	41.6 (8.91)	46.0 (10.33)
Median	43	44
Range	26 – 55	31 – 60
Sex, n (%)		
Male	16 (48.5)	2 (33.3)
Female	17 (51.5)	4 (66.7)
Race, n (%)		
White	24 (72.7)	5 (83.3)
Black or African American	9 (27.3)	0
American Indian or Alaska native	0	1 (16.7)
Ethnicity, n (%)		
Hispanic	3 (9.1)	0
Non-Hispanic	30 (90.9)	6 (100)
Weight, kg		
Mean \pm SD	95.0 (23.84)	76.8 (20.11)
Median	92.1	78.1
Range	40 – 142	53 – 108
Height, cm		
Mean \pm SD	169.5 (9.05)	168.9 (10.01)
Median	167.6	166.2
Range	150 – 185	158 – 185
Body mass index, kg/m ²		
Mean \pm SD	33.0 (7.91)	26.9 (7.03)
Median	33.7	25.9
Range	15 – 50	19 – 40

Of the 33 patients in MSE Dose Group 1 who received study medication, 31 (93.9%) completed both periods of the study. One discontinued BBUP because of an AE and one discontinued full μ -opioid agonist due to being lost to follow-up. Of the six patients in MSE Dose Group 2, five (83.3%) completed the study. One patient discontinued after the first treatment period (BBUP) and was lost to follow-up.

Demographics

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.

Withdrawal Analyses

Thirty-five patients were evaluable for opioid withdrawal; one completer in MSE Dose Group 2 was excluded due to major protocol violation. Only two patients in MSE Dose Group 1 met the definition for opioid withdrawal; one experienced withdrawal with both BBUP and full μ -opioid agonist and the other with full μ -opioid agonist only. None of the six patients in MSE Dose Group 2 met the definition for withdrawal. In MSE Dose Group 1, the mean of maximum COWS score over the 24-hour period on BBUP was lower than on full μ -opioid agonist (4.6 vs 5.3), but the median maximum COWS scores were identical (4.0). Similarly, in MSE Dose Group 2, the mean maximum COWS score was lower on BBUP than on full μ -opioid agonist (5.5 vs 6.3), whereas the median COWS score was also slightly lower on BBUP than on full μ -opioid agonist (6.0 vs 6.5; Table 3). Mean change from baseline in COWS total score during the 24-hour study periods was similar for both treatment groups, as depicted in Figure 2. For both study treatments in MSE Dose Group 1, COWS scores were low during the 4 to 6 hours postdose 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 3. The sample size in MSE Dose Group 2 was too small to analyze.

Table 3 Comparison of maximum COWS total score (per-protocol population)

MSE dose group	Statistic	BBUP	Full μ -opioid agonist*	P value [†]
Group 1	n	31	31	0.7942
80 – 160 mg	Mean (SD)	4.6 (3.15)	5.3 (4.42)	
Group 2	n	4	4	0.6155
161 – 220 mg	Mean (SD)	5.5 (1.91)	6.3 (2.50)	

BBUP = buccal buprenorphine; CI = confidence interval; COWS = Clinical Opiate Withdrawal Scale; MSE = morphine sulfate equivalent.

*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.

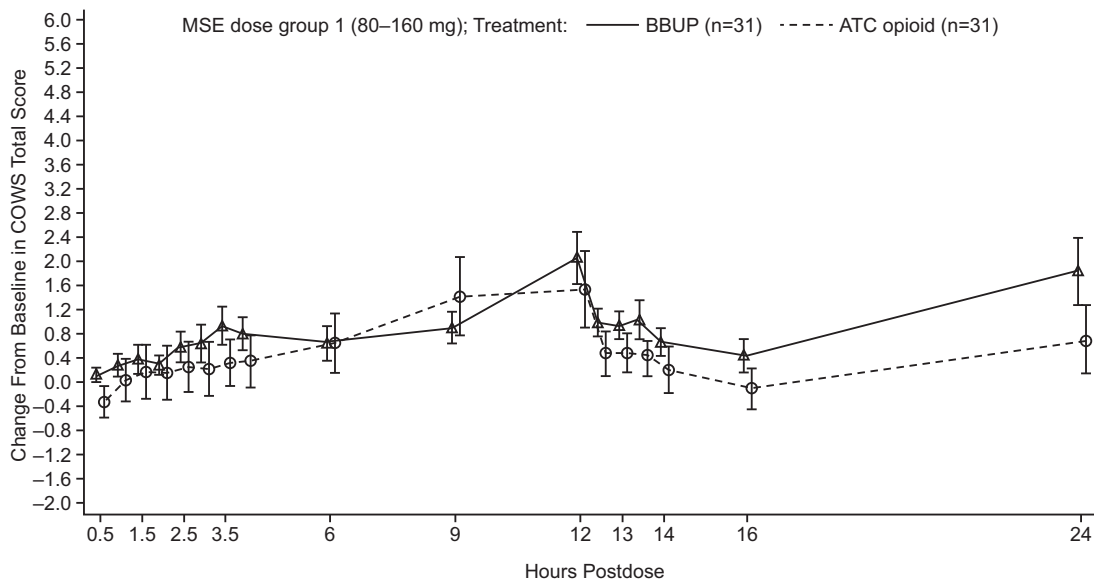


Figure 2 Mean (\pm SE) change from baseline of COWS at selected time points, per-protocol population. ATC=around-the-clock; BBUP=buccal buprenorphine; COWS = Clinical Opiate Withdrawal Scale; MSE = morphine sulfate equivalent.

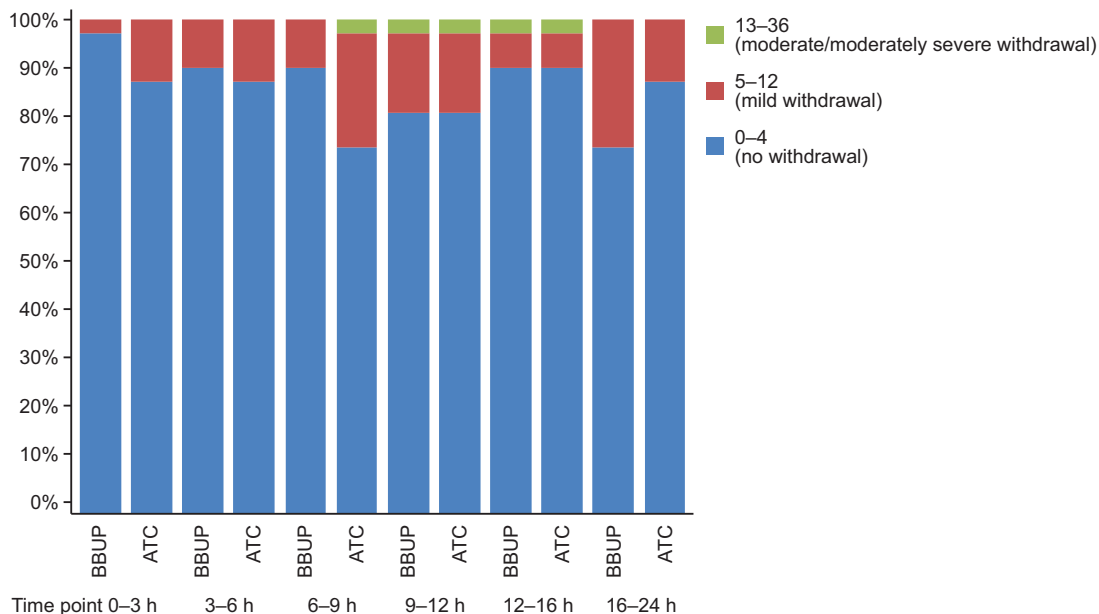


Figure 3 Percent of patients with each COWS category at selected time points (80- to 160-mg MSE cohort, per-protocol population). ATC=around-the-clock; BBUP = buccal buprenorphine; COWS = Clinical Opiate Withdrawal Scale; MSE = morphine sulfate equivalent.

Pain Scores

Similar results were observed for the NRS pain assessments (Figure 4). There was no change from baseline in

mean NRS scores through 9 hours, followed by slight increases from 9 to 12 hours that declined with the second dose. The sample size for MSE Dose Group 2 was too small to analyze.

Full μ -Opioid Agonist to Buccal Buprenorphine Switch

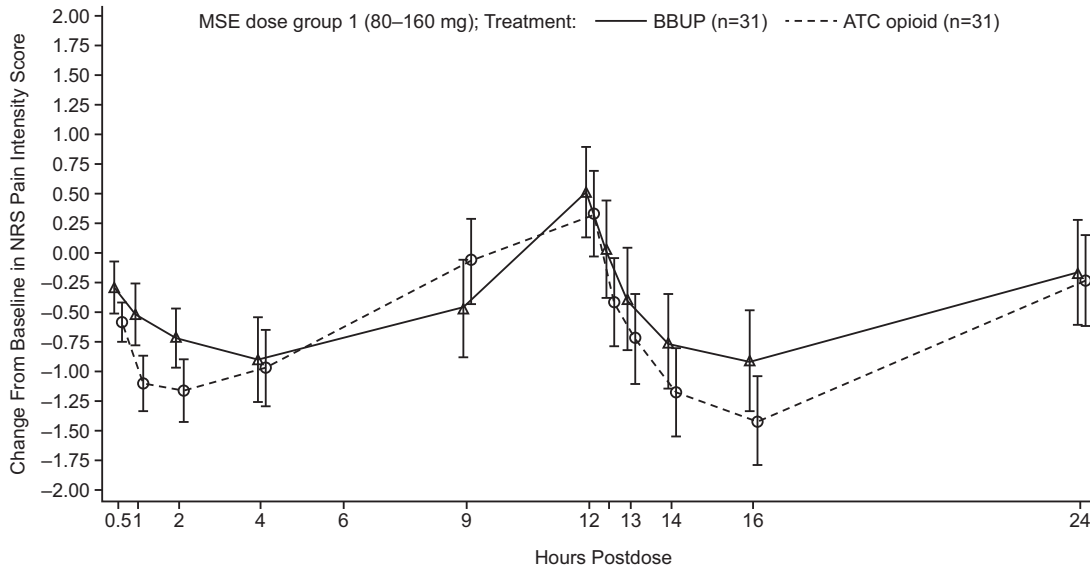


Figure 4 Mean (\pm SE) change from baseline of NRS pain intensity score at selected time points, per-protocol population. ATC = around-the-clock; BBUP = buccal buprenorphine; MSE = morphine sulfate equivalent; NRS = numerical rating scale.

Safety

Adverse events are summarized in Table 4. In MSE Dose Group 1, 18 patients (56.3%) had at least one AE during BBUP treatment, and 13 patients (40.6%) had at least one AE during full μ -opioid agonist therapy. Discontinuations due to AEs occurred with one patient during treatment with BBUP and three patients during ATC treatment. In MSE Dose Group 2, only one patient experienced an AE of drug withdrawal syndrome during BBUP treatment.

In MSE Dose Group 1, the percent of patients with AEs considered related to treatment was 31.3% (10 patients) with BBUP and 21.9% (7 patients) with full μ -opioid agonist. The most frequent AEs with BBUP were headache (19%); vomiting (13%); and nausea, diarrhea, and drug withdrawal syndrome (each 9%). The most frequent AEs with full μ -opioid agonist were headache (16%), drug withdrawal syndrome (13%), and nausea (6%).

No deaths occurred during the study; one patient in MSE Dose Group 1 experienced serious AEs of chest pain and dyspnea when treated with buprenorphine. No clinically meaningful trends were noted in laboratory test results, vital signs, physical examination findings, or C-SSRS.

Discussion

Buprenorphine is a partial agonist at the μ -opioid receptor agonist and an antagonist at the κ receptor, with high affinity binding and slow dissociation from receptors, as well as low intrinsic activity at the μ -opioid receptor [21]. It is possible that administration of buprenorphine to patients with a high percentage of μ -opioid receptors occupied by a full μ -agonist could result in displacement of the full

agonist [21] and precipitate opioid withdrawal. Nevertheless, opioid rotation is an important strategy for pain management in patients who require chronic opioid therapy [23]. This randomized, double-blind, active-controlled study was designed to evaluate the risk of withdrawal syndrome with doses of BBUP administered 8 to 12 hours after the last dose of full μ -opioid agonist. Some important aspects of the study design were inclusion of opioid-dependent patients requiring ≥ 80 mg MSE and documented withdrawal symptoms following a naloxone challenge. In addition, this was a crossover study design in which patients received two doses of BBUP at approximately 50% of their MSE dose and two doses of active full μ -opioid agonist at 50% of their prescribed total daily dose, allowing for direct comparison of withdrawal effects from the two treatments in the same patients.

For the primary efficacy analysis, opioid withdrawal was defined as a maximum COWS total score that was at least 13 or the patient requiring rescue medication for withdrawal symptom management. Only two patients experienced withdrawal during one or both study treatments, both in the MSE Dose Group 1 stratum (80–160 mg). The mean maximum COWS scores did not show any significant difference between full μ -opioid agonist and BBUP ($P = 0.79$). Similarly, there was no change from baseline in mean pain NRS scores through 9 hours postdose. The data did not suggest any difference in opioid withdrawal following BBUP and full μ -opioid agonist administered at 50% of the therapeutic dose. Thus, patients can rotate from a full μ -opioid agonist to BBUP in the 80- to 160-mg MSE dose range without any greater risk of precipitating withdrawal than would be expected when switching to another opioid. Administration of 300- or 450- μ g doses of BBUP 8 to 12 hours after the last dose of full μ -opioid agonist was

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	Full μ -agonist* n = 32	Overall n = 33	BBUP n = 6	Full μ -agonist* n = 5	Overall n = 6
At least 1 TEAE	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 (3.0)	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 (3.0)	0	0	0
Hypoxia	0	1 (3.1)	1 (3.0)	0	0	0

BBUP = buccal buprenorphine; TEAE = treatment-emergent adverse event.

*Morphine sulfate or oxycodone. At each level of patient summarization, a patient is counted once if the patient reported one or more events (n).

not associated with a higher incidence of serious AEs, AEs leading to discontinuation, or treatment-emergent AEs overall compared with the 50% dose of the prescribed full μ -opioid agonist.

One limitation of this study is that the full μ -opioid agonists used in this study and buprenorphine are different molecules with different receptor affinities; it cannot be stated unequivocally that the doses were comparable. As in all opioid conversions, the 50% MSE represents a best estimate. Second, all subjects were converted from morphine or oxycodone, so results may not be applicable to other opioids. In addition, the prespecified calculation of the odds ratio of buprenorphine to full μ -opioid agonist could not be calculated because of the small number of patients who met the definition for opioid withdrawal. Furthermore, no conclusions can be drawn from the high-dose cohort because of the small sample size. Overall, the results suggest that switching patients to a 50% MSE dose of BBUP is comparable in safety and tolerability to reducing a patient to a 50% MSE dose of their current full μ -opioid agonist therapy.

Conclusions

Chronic pain patients treated with around-the-clock full μ -opioid agonist therapy can be switched to buccal buprenorphine (a partial μ -opioid agonist) at approximately 50% of the full agonist dose without an increased risk of opioid withdrawal or loss of pain control.

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