Evaluation of the Pharmacokinetics of Single- and Multiple-Dose Buprenorphine Buccal Film in Healthy Volunteers

Stephen A. Bai, PhD[1,*]; Qinfang Xiang, PhD[1]; and Andrew Finn, PharmD[2]

[1]*Endo Pharmaceuticals Inc., Malvern, Pennsylvania; and* [2]*BioDelivery Sciences International Inc., Raleigh, North Carolina*

ABSTRACT

Purpose: Buprenorphine, a partial μ-receptor agonist, is approved for the management of moderate to severe pain, but it has low oral bioavailability. Two open-label studies were performed to determine the pharmacokinetic profile of buprenorphine from buccal film formulations of buprenorphine.

Methods: Both studies enrolled healthy volunteers, aged 18 to 55 years, who received concurrent oral naltrexone to reduce adverse events (AEs); subjects with a history or evidence of substance abuse or current use of any product affecting cytochrome P450 3A4 activity were excluded. The first study (n = 25) was a 5-period crossover trial with 4 single doses (75 and 300 and 300 and 1200 μg) of 2 formulations (F14 and F24) of buccal buprenorphine (BBUP) and a 300-μg intravenous dose of buprenorphine with a 7-day washout between periods. In the second study, each subject (n = 10) received 6 doses of 4 BBUP strengths (60, 120, 180, and 240 μg BID) in a dose-escalation design. Plasma concentrations of buprenorphine and norbuprenorphine were assayed, and pharmacokinetics were summarized with descriptive statistics and analyzed by using a linear mixed effects model (single-dose study). AEs were recorded.

Findings: In the single-dose study, the 2 formulations exhibited comparable bioavailability of 46% to 51% that was independent of dose, with a single buprenorphine peak concentration from each BBUP dose occurring at 2.5 to 3 hours. The mean buprenorphine C_{max} across the doses ranged from 0.17 ng/mL for the 75-μg dose to 1.43 ng/mL for the 1200-μg dose. $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} were proportional to the dose of BBUP administered. C_{max} of norbuprenorphine after BBUP administration was approximately one tenth that of buprenorphine C_{max}. In the multiple-dose study, steady state was reached within 3 days of BID dosing. There was a linear increase in exposure across the dose range from 60 to 240 μg BID. Treatment-emergent AEs in both studies were consistent with those reported with opiate administration to healthy volunteers.

Implications: The absolute bioavailability of BBUP was 46% to 51% across a 16-fold dose range, with dose-proportional increases in systemic exposure. Apparent steady-state conditions occurred within 3 days of dosing. These pharmacokinetic results suggest that therapeutic buprenorphine plasma concentrations can be obtained with BBUP across a wide dose range in a shorter time than other (eg, transdermal) dosage forms. (*Clin Ther.* 2016;▮:▮▮▮–▮▮▮)

Key words: bioavailability, buprenorphine buccal film, pharmacokinetics.

INTRODUCTION

Buprenorphine is a partial μ-opioid receptor agonist used for the treatment of acute and chronic moderate to severe pain[1–5] and opioid dependence.[6–10] It is classified as a Schedule III controlled substance in the United States and has attributes that may provide an improved risk–benefit profile relative to other opioids.[11,12]

Buprenorphine is an effective analgesic with no analgesic ceiling and an analgesic potency reported to be 30 to 115 times greater than that of oral morphine sulfate.[1,11,13–15] It is also an agonist at the opioid receptor-like 1 receptor, activation of which has been

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*Stephen Bai is now retired.

shown to block analgesic tolerance and the rewarding effects of opioids,[1,4,5,16,17] thus resulting in a lower potential for abuse and diversion. In addition, buprenorphine has a lower potential for some adverse events (AEs) typically associated with opioid use, such as constipation[18–20] and respiratory depression.[5,21,22]

Currently approved formulations of buprenorphine for the treatment of pain include intravenous (IV)[†] and transdermal[‡] formulations.[11,23,24] The bioavailability of sublingual buprenorphine[§] (discontinued in 2012 in favor of the buprenorphine-naloxone combination product[‖]), which is not approved for the treatment of pain, is ~20%.[25,26] Transdermal buprenorphine has a similarly low bioavailability (~15%),[23] with limited capacity for dose titration; it is available in the United States in a narrow dose range of 5 to 20 μg/h as 7-day patches. Moreover, only doses in the 10- to 20-μg/h range have demonstrable efficacy, and the highest dose may not be effective for some individuals requiring a morphine sulfate–equivalent dose of >80 mg/d.[27] An alternate buprenorphine formulation that permits titration over a wider dose range could help more patients achieve well-tolerated and effective analgesia.

A buprenorphine buccal-soluble formulation[#] has recently been approved for treating chronic pain severe enough to require daily, around-the-clock, long-term opioid therapy and for which alternative treatment options are inadequate.[28] Buccal buprenorphine (BBUP) uses a BioErodible MucoAdhesive (BEMA) delivery technology composed of flexible, water-soluble polymeric films that adhere to the moist buccal mucosa and then erode. The BEMA delivery system is a bilayer dose form that facilitates transmucosal delivery and minimizes the amount of buprenorphine dissolved in the saliva and swallowed. The transmucosal buprenorphine dose delivered by BBUP is determined by the film size (surface area) and formulation.

The present article summarizes the results of 2 Phase I pharmacokinetics (PK) studies in healthy volunteers. The first study compared the single-dose PK of buprenorphine and norbuprenorphine from 2 formulations (F14 and F24) across a 16-fold range of doses. The formulations differed in buprenorphine concentration by a factor of 5 (F14 > F24 on a percent weight/weight basis). The second study examined the multiple-dose PK from a single formulation of BBUP (F24) with doses administered every 12 hours and the dose level increased every 3 days.

SUBJECTS AND METHODS

Participants

Both studies included healthy male and female volunteers, aged 18 to 55 years, weighing at least 59 kg and having a body mass index ≥18 and ≤30 kg/m^2. Eligible subjects were nonsmokers with normal buccal mucosa who had no significant psychiatric or physical disorder; had no history or evidence of substance abuse, dependence, or opioid-induced vomiting; and were not using any product affecting cytochrome P450 3A4 activity. For the multiple-dose study only, participants taking any class IA or class III antiarrhythmic medications were excluded.

All study participants were informed of the nature and risks of participating in their respective study. All subjects provided written informed consent before participation.

Study Design

Single-Dose Study

The first study was an open-label, randomized, single-dose, 5-sequence, 5-period crossover trial. Participants were randomized to receive a sequence of 5 treatments based on a 5 × 5 Latin square design. In each treatment period, participants received a single dose of study drug applied to the oral mucosa after an overnight fast. Participants were confined to the clinic for 3 overnight stays, and there was a minimum 7-day washout between treatment periods. Four single doses of BBUP were applied to the buccal mucosa. Two formulations (F14 and F24) and 2 doses of each (F14, 300 and 1200 μg; F24, 75 and 300 μg) were administered (Table I). The fifth treatment was an IV injection of 300 μg of buprenorphine (buprenorphine hydrochloride, equivalent to 0.3 mg of buprenorphine per milliliter) infused over 2 minutes. The IV dose was included to allow assessment of absolute

[†]Trademark: Buprenex® (Reckitt Benckiser Pharmaceuticals Inc, Richmond, Virginia).

[‡]Trademark: Butrans® (Purdue Pharma LP, Stamford, Connecticut).

[§]Trademark: Subutex® (Reckitt Benckiser Pharmaceuticals Inc).

[‖]Trademark: Suboxone® (Reckitt Benckiser Pharmaceuticals Inc).

[#]Trademark: BELBUCA™ (Endo Pharmaceuticals Inc., Malvern, PA).