

BEMA[®] BUPRENORPHINE PRODUCED EFFECTIVE ANALGESIA IN A PHASE 2 PLACEBO-CONTROLLED TRIAL OF MODERATE TO SEVERE PAIN FOLLOWING DENTAL EXTRACTION

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Purpose

BEMA[®] Buprenorphine (BEMA-Bup), a partial mu-opioid agonist in development for moderate to severe pain, comprises a small, bilayered, dissolvable polymer film formulated with the Schedule III analgesic buprenorphine for buccal application. BEMA-Bup employs BioErodible MucoAdhesive (BEMA[®]) delivery technology and facilitates buccal delivery of buprenorphine, which is poorly bioavailable when administered orally. Buprenorphine, widely used outside the US, has potential for less abuse and addiction than Schedule II opioids. This Phase 2 trial compared analgesic effects of escalating doses of BEMA-Bup with those of placebo and a standard opiate.

Method

Subjects with at least moderate postsurgical (baseline) pain intensity on a 4-point categorical scale and ≥ 5 on a 0- to 10-point Numeric Rating Scale within 5 hours of completing third molar extraction under local anesthesia received one of 5 treatments in this double-blind, double-dummy, parallel-group study: **placebo** (n=30); **BEMA-Bup 0.25 mg Formulation 2** ("low" dose; n=31); **BEMA-Bup 0.5 mg Formulation 2** ("medium" dose; n=30); **BEMA-Bup 0.5 mg Formulation 1** ("high" dose; n=31); or **oxycodone 5 mg** overencapsulated oral tablet, active control; n=31). Note that the buprenorphine bioavailability of BEMA-Bup Formulation 2 is approximately 63% that of Formulation 1, a difference that accounts for the distinction between the high dose and the medium dose. Analgesic assessments were recorded at baseline and at predetermined time points through 24 hours postdose.

Results

Values for the time-weighted Sum of Pain Intensity Difference from baseline to 8 hours postdose (SPID-8) increased with dose in the BEMA-Bup groups. The difference between BEMA-Bup and placebo in SPID-8 approached significance for BEMA-Bup 0.5 mg Formulation 1 in the last observation carried forward (LOCF) primary analysis (p=0.0809) and was statistically significant in the baseline observation carried forward (BOCF) sensitivity analysis (p=0.0334). Values for time-weighted Total Pain Relief over 8 hours postdose (TOPAR-8) increased with dose in the BEMA-Bup groups with statistically significant differences versus placebo for BEMA-Bup 0.5 mg Formulation 1 in both the LOCF analysis (p=0.0242) and the BOCF analysis (p=0.0164). The overall incidence of adverse events increased with BEMA-Bup dose: 35.5% with BEMA-Bup 0.25 mg Formulation 2, 70.0% with BEMA-Bup 0.5 mg Formulation 2, and 83.9% with BEMA-Bup 0.5 mg Formulation 1. The overall incidence of adverse events was 26.7% with placebo. The pattern of adverse events was typical of strong opioid doses administered to subjects who are not opioid tolerant and was consistent with that in other studies of pain following dental extraction and other studies of opioids. Nausea and vomiting were the most frequently reported adverse events. No deaths, serious adverse events, or premature withdrawals because of adverse events were reported. No subject experienced clinically significant changes from predose to postdose in clinical laboratory parameters or vital signs, electrocardiograms (ECGs), or physical exams. The oxycodone dose was subtherapeutic as it neither elicited effective analgesia nor was associated with significant adverse events.

Conclusions

In this randomized, double-blind, placebo-controlled, Phase 2 trial, BEMA-Bup produced effective analgesia versus placebo in the treatment of moderate to severe pain following dental extraction as

evidenced by dose-related increases in both SPID-8 and TOPAR-8 values. The adverse event profile is typical of strong opioid doses administered to subjects who are not opioid tolerant. The efficacy, safety, and tolerability profiles of BEMA-Bup are being further investigated in ongoing Phase 3 clinical development.