Pharmacokinetics of Dexmedetomidine after a Single Sublingual Dose of BXCL501 in Patients with Agitation Associated with Schizophrenia

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INTRODUCTION

- Dexmedetomidine (DEX), a selective alpha-2 adrenergic receptor agonist being developed for the treatment of agitation associated with schizophrenia and bipolar disorders
- DEX is currently available as IV drug for ICU and procedural sedation
- BXCL501 is a new formulation (orally dissolving film) of dexmedetomidine designed for sublingual [SL] or buccal administration.
- This study characterized the pharmacokinetics (PK), efficacy and safety of DEX after SL administration of BXCL501 in patients with agitation associated with schizophrenia

METHODS

- This was a single ascending dose, placebo-controlled, double blind study (2:1 active/placebo randomization) with option for additional dose in the absence of adequate efficacy
- A total of 135 (90 active, 45 placebo) individuals aged 18-65 years with agitation associated with schizophrenia were enrolled
- Participants received single 20, 60, 80, 120, and 180 mcg doses of BXCL501 or placebo.
- Plasma samples were collected over 24 hours post-dose and analyzed for DEX by validated liquid chromatography with tandem mass spectrometry assay.
- PK parameters were estimated by non-compartmental analysis of the plasma-concentration data using WinNonlin.
- Efficacy was assessed using a variety of measures with change from baseline in PEC score at 2 hours postdose as the primary measure.
- Safety was assessed using a variety of measures including AEs, clinical laboratory tests, vital signs and ECG.

RESULTS

- After administration of BXCL501, plasma levels of DEX were detectable after all doses (Figure 1). Absorption of DEX was rapid with the maximum concentration (C_{max}) achieved on average within 2 hours after dosing.
- Exposure was approximately dose proportional between 20 and 180 mcg doses. **(Figure 1)** DEX was eliminated from plasma with a half-life between 2 and 3 hours.
- Dose-dependent improvements in PEC total scores from baseline at 2 hours post-dose were observed and reached significance with BXCL501 80 mcg, 120 mcg, and 180 mcg with mean changes of -7.3, -9.2, and -10.8 points, respectively, versus -4.5 for placebo. (**Figure 2**)
- There were no serious or severe treatment emergent adverse events (TEAEs) or discontinuations due to AEs. There were 43 TEAEs, 82% of which were mild. The most reported TEAEs were somnolence (81% mild) and dry mouth (100% mild). There were 6 reports of hypotension, 3 of orthostatic hypotension, and 1 of bradycardia, all of which resolved.

Figure 1. 2-hour Plasma Concentration of DEX after a Single-Dose Sublingual BXCL501 Administration normalized to the concentration after the lowest dose (20 mcg) in Patients with Schizophrenia

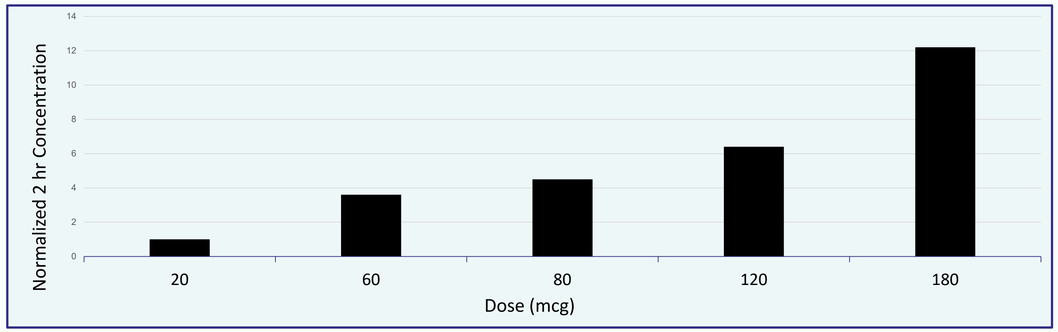
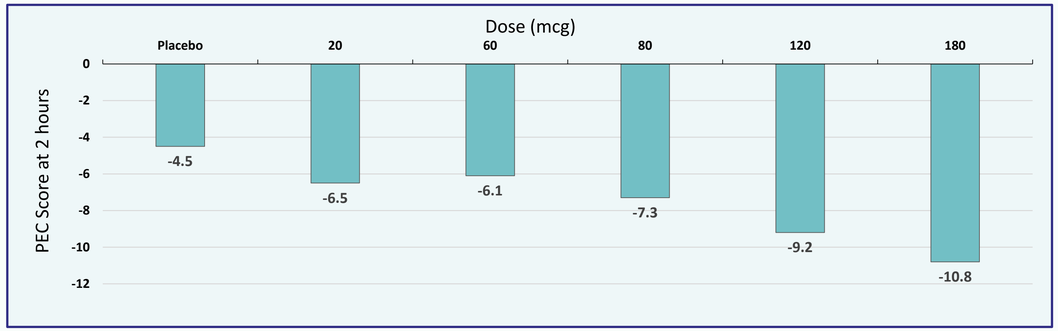


Figure 2. PEC Total Score Change From Baseline at 2 Hours in Patients with Schizophrenia after Sublingual Doses of BXCL501



NOTE: 20 mcg dose group includes 8 of 18 subjects who received a 2nd 20 mcg dose 1 hour after the 1st due to insufficient efficacy.

CONCLUSIONS

- The results demonstrate a dose-dependent increase in exposure of dexmedetomidine after sublingual administration of BXCL501, a new formulation (orally dissolving film) of dexmedetomidine.
- At the doses given, BXCL501 demonstrated dose- and exposure-dependent reduction in agitation in adults with schizophrenia experiencing acute agitation.
- There were no serious or severe TEAEs or discontinuation due to AEs. The majority were mild, the most common being somnolence and dry mouth. There were 6 instances of hypotension (5 mild/1 moderate), 3 of orthostatic hypotension (all mild), and 1 of bradycardia (mild), all of which resolved.
- Results provide data to use in selecting doses for subsequent studies.

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