M72 Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Determine the Efficacy, Safety, and Pharmacokinetics of BXCL501 (Sublingual Dexmedetomidine) in Agitation Associated with Schizophrenia or Related Disorders

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BACKGROUND

Dexmedetomidine (DM) is a selective alpha-2 adrenergic agonist currently marketed as an intravenous (IV) formulation for anesthesia. Because IV drugs are not suitable for administration to agitated patients in emergency rooms, a sublingual formulation of DM (BXCL 501) was developed and tested for its potential efficacy in agitation associated with schizophrenia or related disorders

OBJECTIVES

Primary:

Determine the doses of BXCL501 needed to effectively reduce symptoms of acute agitation associated with schizophrenia, schizoaffective disorder or schizophreniform disorder assessed using the Positive and Negative Syndrome Scale – Excited Component (PEC) change from baseline after drug treatment.

Secondary:

Pharmacokinetics (PK), safety and tolerability of the various film strengths of BXCL501 in patients with acute agitation associated with schizophrenia, schizoaffective disorder or schizophreniform disorder including (a) the duration of calming effect as measured by PEC and ACES; safety profile particularly as measured by vital signs and reports of adverse events

Drug Development Methodology

Prior to this study, 4 studies were conducted with DM in two formulations: (a) an intravenously administer solution (3 studies) and (b) a sublingual formulation. The titles and doses administered in these studies are provided in table1 below:

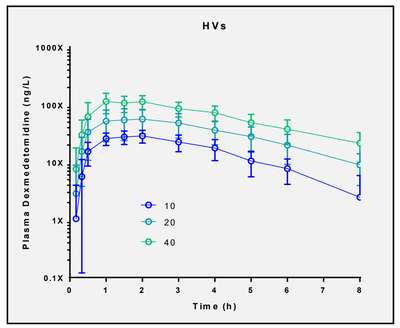
Study Number	Title	Dosing Strategy
BXCEL1	A Phase 1, Randomized, Placebo-controlled, Single Ascending or Descending, Single Site Study of Dexmedetomidine in Healthy Elderly Participants and Patients With Mild Probable Alzheimer's Disease	continuous intravenous (IV) administration until predetermined efficacy and/or safety endpoints (EP) were met.
DEX001	A Phase 1b, Randomized, Placebo-controlled, single ascending or descending, single site study of dexmedetomidine in participants with Schizophrenia	continuous IV administration until predetermined EP were met.
DEX002	A Phase I, Randomized, Placebo-Controlled Trial of the Effectiveness of Dexmedetomidine (DEX) Administered Intravenously for the Treatment of Mild to Moderate Withdrawal in Patients with Opioid Use Disorder	continuous IV administration until predetermined EP were met.
BXCL501-101	Phase 1, randomized, single-blind, placebo-controlled, single ascending dose study of the pharmacokinetics, safety & tolerability of BXCL501 (sublingual film) in healthy adult volunteers	4 sublingual (SL) Dose Groups: 10µg 8 active/4placebo 20µg: 8 active/4 placebo 40µg: 8 active 4 placebo 40µg: 4 active 2 placebo
BXCL501-102	A Phase 1b multicenter, randomized, double-blind, placebo-controlled, single ascending dose study to determine efficacy, pharmacokinetics and safety of BXCL501 in agitation associated with schizophrenia	5 SL dose groups: 20µg: 18 active/9 placebo 60µg: 18 active/9 placebo 80µg: 18 active/9 placebo 120µg: 18 active/9 placebo 180µg: 18 active/9 placebo

RESULTS

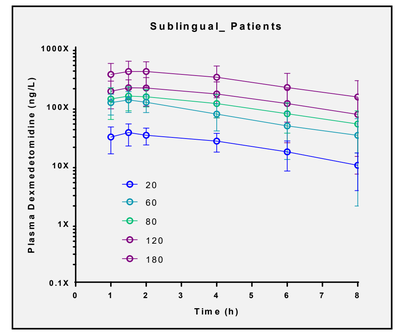
BXCL501-102 Trial Design: This phase 1B study employed a randomized, double-blind, placebo-controlled, multiple single ascending dose design in separate cohorts of males or female adults (18 – 65 years of age) with agitation associated with schizophrenia, schizoaffective or schizophreniform disorder as defined by DSM-5. These subjects could be on a wide range of other psychiatric medication if the dose had been stable for at least 2 weeks. Each cohort consisted of 27 individuals assigned 2:1 to either BXCL 501 or an identical appearing placebo. Each participant met commonly used inclusion and exclusion criteria including being agitated at baseline ion defined as a total score ≥ 14 on the 5 items of the PANSS Excited Component (PEC) (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement) and a score of ≥ 4 on at least 1 of the 5 items. Primary efficacy endpoint was the proportion of subjects in each cohort (BXCL 501 and placebo) who experienced ≥ a 40% reduction in PEC score at 2 hours which is a value that has been used for FDA registration for an anti-agitation indication for other drugs. Safety measures included AEs, clinical laboratory tests, ECG, vital signs (blood pressure and heart & respiratory rate) and level of arousal. Plasma sample were obtained at pre-specified time-points prior to and after dosing for determination of drug concentration. The initial dose was 20 mcg followed by single doses of 60, 80, 120 and 180 mcg.

EXPOSURE

A) Healthy Volunteers



B) Agitated Patients with Schizophrenia



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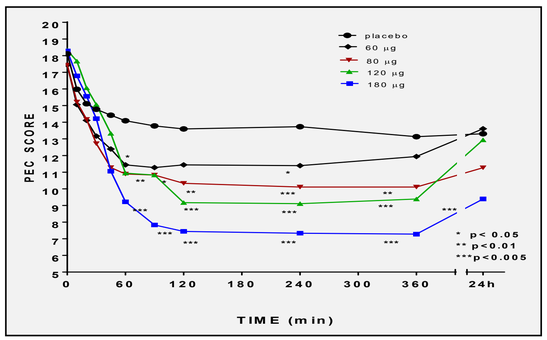
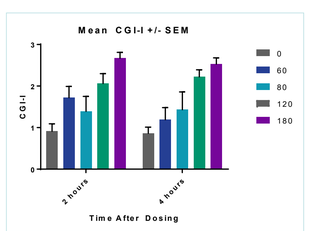
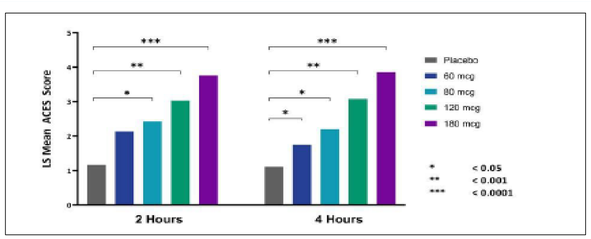


Percentage of Responders (40% Reduction in PEC Score) from Pre-Dose to 24 Hours

Time Post Dose (min)	Dose Group					
	Placebo N=45	20 µg N=18	60 µg N=18	80 µg N=18	120 µg N=18	180 µg N=18
PreDose	0	0	0	0	0	0
10	13%	0%	11%	6%	6%	6%
20	16%	0	22%	22%	6%	6%
30	22%	11%	28%	22%	17%	11%
45	18%	17%	33%	39%	28%	44%
60	22%	28%	39%	56%	56%	56%
90	27%	39%	50%	50%	50%	72%
120	31%	56%	39%	56%	67%	89%
240	20%	61%	44%	61%	67%	94%
360	29%	61%	39%	56%	61%	94%
1440	20%	44%	22%	40%	33%	78%



SAFETY



Agitation-Calmness Evaluation Scale (ACES), where 1 indicates marked agitation; 2 - moderate agitation; 3 - mild agitation; 4 - normal behavior; 5 - mild calmness; 6 - moderate calmness; 7 - marked calmness; 8 - deep sleep; and 9 – unarousable.z

Effects on blood pressure (BP) and heart rate (HR) were subject to special safety monitoring with pre-specified thresholds: assessments were repeated for systolic (SBP) or diastolic (DBP) less than 90 mmHg, or 60 mmHg (respectively), and for HR below 50 bpm. Although there were minor transient excursions in BP in 17 subjects across all dose groups, the effect was not dose-related and included placebo subjects.

HR values below 50 bpm were only observed in 3 subjects on placebo and 2 subjects at 120 mcg assessed from time of dose through the next day. These effects were minor, transient, rapidly normalized and no arrhythmias occurred. All subjects with lower HR and BP values normalized without medical intervention and required no further monitoring.

There were no clinically meaningful changes in resting HR, or SBP or DBP for the range of doses tested. Mild hypotension was observed in 1 subject at 120 mcg, and 4 subjects in the 180 mcg dose group suggesting a dose relationship. All were judged of mild to moderate severity and all subjects were able to continue ADLs and complete the study without medical intervention

CONCLUSIONS

BXCL 501 produced a rapid (within 1 hour, hr) reduction in agitation which was sustained for up to 6 hr at highest doses . All doses were safe and well tolerated. The duration of the effect is longer than what would be anticipated based on the plasma half-life of the drug.

No clinically meaningful adverse effects occurred on any dose so a number needed to harm was not calculatable.

Based on response being defined as a 40% reduction in PEC scores, the proportion of responders on 180 mcg vs placebo were 56% vs 22% at 1 hr, 89% vs 31% at 2 hr, 94% vs 29% at 6 hr, and 78% vs 20% at 24 hr. The number needed to treated for efficacy was: < 3 at 1 hr and < 2 at all other time points (percentage responder table).

Participants with agitation were capable of tolerating concentrations which were 5 – 10 fold higher than those tolerated by normal controls (exposure figures). Psychiatric drug developers thus must keep this possibility in mind when going from health volunteers to agitated patients.

In summary, the results of this study supports the further development of BXCL 501 with its novel mechanism as a treatment of agitation in patients with schizophrenia and possibly other such conditions.

For additional information on the preclinical data with the drug, please refer to the following poster presented at this meeting: De Vivo, M et al: T230 Dexmedetomidine– Highly Favorable Pharmacokinetic and Pharmacological Features for a CNS Therapeutic Drug - Adaptation to Stress

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