Double-blind, Placebo-controlled Multiple Ascending Dose Study of BXCL501 with Concomitant Treatment with Antidepressant in Healthy Volunteers

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Background

- BXCL501 (dexmedetomidine micro deposited onto a sublingual film) is approved for the acute treatment (single dose) of agitation associated with schizophrenia and bipolar disorders.
- BXCL501 has been dosed in multiple clinical trials but always as a single acute dose.
- Other alpha2-adrenergic receptor agonists are approved for ADHD, opioid withdrawal and hypertension. Some of these indications necessitate repeat daily dosing.
- The purpose of this Phase I study was to determine the safety profile of BXCL501 after 7 days of repeat dosing in healthy volunteers. The results of this study were planned to select the dosing regimen for any next trials that would necessitate repeat dosing and/or combination with antidepressant therapy.
- A secondary objective of this study was to determine if the plasma exposures change with repeat dosing.

Methods

- The current study was a Phase I, single-site, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study assessing the safety and pharmacokinetics (PK) of BXCL501 in healthy participants when administered alone or concomitantly with an antidepressant
- The primary objective was to first determine the maximum tolerated dose (MTD) of BXCL501 alone in healthy participants and then to determine if this MTD was adequately tolerated when given with an effective dose of a serotonin-norepinephrine reuptake inhibitor duloxetine.
- Participants were enrolled in sequential cohorts. Each cohort was treated for 7 days, followed by 3 days of follow-up.
- Subsequent cohorts were enrolled after thorough review of the safety data from the preceding cohort and the determination that the dose for the just treated cohort did not exceed an MTD.

- ➢ Cohort 1: 30 µg or placebo (12 active; 6 placebo) administered every morning (qAM).
- ➢ Cohort 2: 60 µg or placebo (12 active; 6 placebo) administered qAM.
- ➢ Cohort 3: 80 µg or placebo (12 active; 6 placebo) administered qAM.
- ➢ Cohort 4: 30 µg administered qAM and 60 µg administered every evening (qHS), or placebo (12 active; 6 placebo).
- ➢ Cohort 5: 40 µg administered qAM and 80 µg administered qHS, or placebo (12 active; 6 placebo).
- ➢ Cohort 6: 120 µg or placebo (12 active; 6 placebo) administered qAM.
- ➢ Cohort 7: 30 mg duloxetine twice daily (BID) in addition to the doses of BXCL501 60 µg administered qAM and 80 µg administered qHS (dosing determined based on data from previous cohorts)

- Criteria for a dose exceeding MTD included clinically significant number of participants experiencing any AE of special interest, including excessive sedation (defined as ACES= 9), somnolence, dizziness, hypotension, orthostasis, or bradycardia and confirmed by review of all safety data for studied cohorts.
- A secondary objective was to characterize the pharmacokinetics (PK) of BXCL501 during repeat dosing regimens.
- An additional objective was to assess any withdrawal signs that occurred after 7 days of treatment, including tachycardia, increase in blood pressure, any nausea/vomiting, and agitation (ACES score of 1 or 2).

Results

- 125 participants were randomized, of whom 118 completed the study.
- Withdrawal of consent was the sole reason for discontinuation in the 7 participants who did not complete the study (3 in pooled placebo group and 1 each in active arms of Cohorts 2, 3, 4, and 5)

Safety

- According to pre-specified criteria, no dosing cohort exceeded MTD.
- No death or serious adverse event (SAE) were reported during the study.
- No AE required the withdrawal of a participant during the study period.
- All AEs were mild or moderate in intensity. The most common TEAE was mild orthostatic hypotension (**Table 1**).
- The combination duloxetine 30 mg BID + BXCL501 60 µg qAM + 80 µg qHS did not lead to the development of more AEs than the other treatment groups.

Table 1. Number (percent) of patients with AEs occurring in more than one patient in any active treatment group

AE	Pooled placebo (n=42)	30 µg qAM (n=12)	60 µg qAM (n=13)	30 µg + 60 µgµg (n=13)	40 µg + 80 µg (n=12)	80 µg qAM (n=13)	120 µg qAM (n=12)	Duloxetine BID +60 µg + 80 µg (n=8)
ALL	16 (38.1%)	4 (33.3%)	12 (92.3%)	6 (46.2%)	5 (41.7%)	9 (69.2%)	8 (66.7%)	5 (62.5%)
Lack of satiety	3 (7.1%)	0	4 (30.8%)	0	0	0	0	0
Dizziness	1 (2.4%)	0	2 (15.4%)	1 (7.7%)	0	1 (7.7%)	1 (8.3%)	1 (12.5%)
Headache	2 (4.8%)	2 (16.7%)	2 (15.4%)	0	1 (8.3%)	2 (15.4%)	1 (8.3%)	0
Somnolence	3 (7.1%)	0	10 (76.9%)	0	0	0	1 (8.3%)	0
Hypotension	0	0	0	0	0	2 (15.4%)	4 (33.3%)	1 (12.5%)
Orthostatic hypotension	10 (23.8%)	2 (16.7%)	7 (53.8%)	4 (30.8%)	3 (25.0%)	8 (61.5%)	7 (58.3%)	4 (50%)

- Changes in ECG numeric parameters were observed in some of the groups, but no dose-related relationship or clinically relevant pattern were observed.
- There was no clinically significant abnormality in ECG parameters according to Investigator's assessment.

- Levels of agitation and sedation were measured by Agitation-Calmness Evaluation Scale (ACES), Most of the participants in each group had a normal behavior (score=4) during the whole study period with few experiencing significant sedation (**Table 2**).
  - There were no participants with ACES score of 9 (unarousable deep sleep)

Table 2. Number of patients with significant or excessive sedation at any point during the trial

Score	Pooled placebo (n=42)	30 µg qAM (n=12)	60 µg qAM (n=13)	30 µg + 60 µg (n=13)	40 µg + 80 µg (n=12)	80 µg qAM (n=13)	120 µg qAM (n=12)	Duloxetine BID +60 µg + 80 µg (n=8)
7 (marked calmness)	1	0	0	0	0	0	1	0
8 (deep sleep)	2	0	1	0	0	1	0	1
9 (unarousable)	0	0	0	0	0	0	0	0

Withdrawal/Rebound

- Tachycardia was the only potential withdrawal sign/symptom observed, except for one case of vomiting (**Table 3**).
  - No participant experienced marked or moderate agitation (ACES scores of 1 or 2, respectively) or systolic hypertension, which were also prespecified as symptoms of withdrawal/rebound.
- None of the study participants experienced signs or symptoms of withdrawal/rebound phenomena on 2 or more consecutive days.

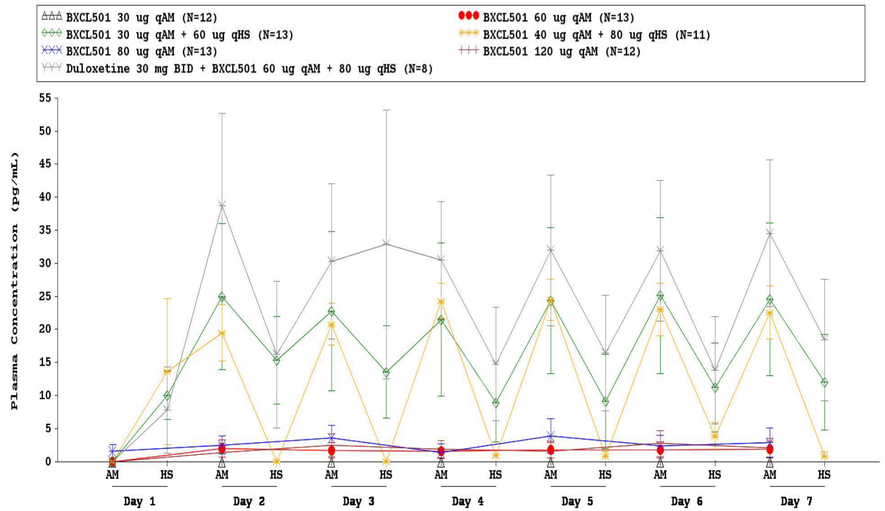
Table 3. Number (%) of patients with at least one potential withdrawal/rebound sign or symptom during the 3-day post-treatment period

Potential withdrawal phenomenon	Pooled placebo (n=42)	30 µg qAM (n=12)	60 µg qAM (n=13)	30 µg + 60 µg (n=13)	40 µg + 80 µg (n=12)	80 µg qAM (n=13)	120 µg qAM (n=12)	Duloxetine BID +60 µg + 80 µg (n=8)
Any	6 (14.3%)	0	1 (7.7%)	4 (30.8%)	1 (8.3%)	2 (15.4%)	3 (25.0%)	1 (12.5%)
Tachycardia	6 (14.3%)	0	1 (7.7%)	4 (30.8%)	1 (8.3%)	2 (15.4%)	3 (25.0%)	1 (12.5%)
Nausea/vomiting	0	0	0	0	0	1 (7.7%)	0	0

Pharmacokinetics

- After sublingual administration, the dexmedetomidine absorption was rapid with peak plasma concentration achieved at a median time of 2h post-dose at any dose.
- Dexmedetomidine was eliminated with a short half-life of about 2 to 3 hours.
- With repeat daily dosing, peak plasma concentrations and plasma exposure of dexmedetomidine increased with the dose between 30 and 140 µg BXCL501 either as a single dose (qAM) or split dosing (qAM+qHS).
- No accumulation in plasma was observed during 7 days of treatment after QD administration or BID administrations with the different dose combinations evaluated (**Figure 1**)

Figure 1. Dexmedetomidine arithmetic mean (±SEM) trough plasma concentration-time profiles



Summary

- **Overall, the safety results showed that repeat administration of BXCL501 at the doses of 30 µg - 140 µg over 7 days in single or divided doses were safe and well tolerated**
- **Similarly, repeat 7-day administration of duloxetine 30 mg BID + BXCL501 60 µg qAM + BXCL501 80 µg qHS was safe and well tolerated**
- **Despite the high frequency of orthostatic hypotension in all groups, this frequent AE was always classified as mild to moderate in intensity and never led to participant discontinuation.**
- **Dexmedetomidine also showed consistent PK profile across the doses and dosing regimens tested in the study.**
- **No participant met the prospective criteria for experiencing a withdrawal syndrome (symptoms of withdrawal/rebound on at least 2 consecutive days).**

Disclosures: All authors are employees and hold equity in BioXcel Therapeutics

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