A Phase Ib/II Multicenter, Randomized, Double Blind, Placebo Controlled, Ascending Dose Finding Study of BXCL501 in Agitation Associated with Dementia

Robert Risinger, MD[1], Lavanya Rajachandran, PhD[1], Heather Robison, MPP[1]

[1]BioXcel Therapeutics, New Haven, CT, USA

Background

- Currently, treatment of acute agitation for the elderly with dementia includes antipsychotics and benzodiazepines. Though efficacy has been demonstrated for each of these agents, older people are more sensitive to the side effects produced by these drugs
- There is a need for an alternative non-invasive, potentially safer medications which would produce a calming effect that would allow patients with acute agitation and dementia to better be able to participate in their care and treatment
- BXCL501, a sublingual film formulation of dexmedetomidine, a highly selective α2 adrenoceptor agonist, is currently approved in adults for the acute treatment of agitation associated with schizophrenia or bipolar disorder as IGALMI. The objective of this study was to determine the appropriate dose of BXCL501 for initiating Phase 3 trials in elderly patients with dementia.

Methods

- Randomized, double-blind, placebo-controlled, multiple ascending dose study assessing safety, tolerability and efficacy of BXCL501 dosing in elderly adults with acute agitation associated with dementia (TRANQUILITY I).
- Fifty patients were initially randomized to placebo, 30, and 60ug doses of BXCL501 (part A), and then an additional 46 patients were randomized in a 1:1 ratio to receive BXCL501 40 µg or matching placebo (**Figure 1 and Table 1**).

Figure 1: Overall Design of the TRANQUILITY I Phase 1b/2 Trial in Dementia

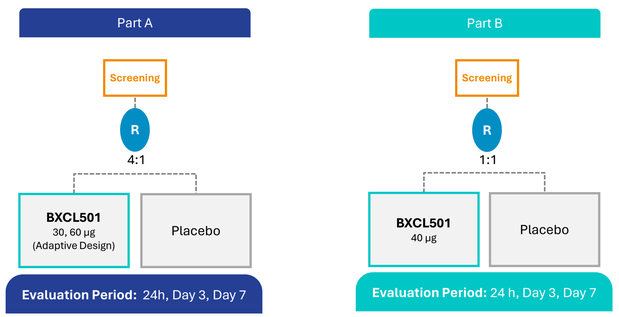


Table 1: Key Inclusion & Exclusion Criteria

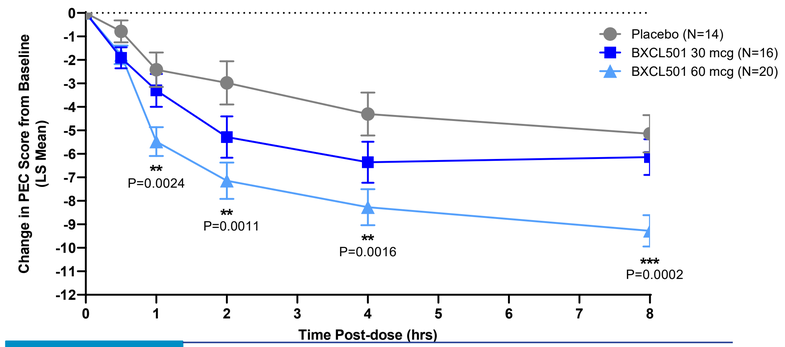
Inclusion Criteria	Exclusion Criteria
• Males & females aged 65 years or older • Diagnosis of dementia using DSM-5 criteria • History of acute agitation that impairs social activities, requires staffing, medical intervention, or impairs daily living • Total score of ≥8 on the 4 items* comprising the PAS at screening and baseline • Score of ≥2 on at least 1 of the 4 items on the PAS at baseline	• Agitation caused by acute intoxication or positive identification of non-prescription drugs during urine screening • Use of benzodiazepines, other sedatives, hypnotics, or antipsychotics 4 hours before study treatment • Treatment with alpha-1 noradrenergic blockers or alpha-adrenergic antagonists within 8 hours prior to dosing • For Part B: Patients who have dementia associated with Parkinson's disease and/or Lewy Body Disease, if etiology of dementia is known.

* Items were aberrant vocalization, motor agitation, aggressiveness & resisting care on Pittsburgh Agitation Scale (PAS)

Results

- In Part A and Part B, 96 patients were enrolled and randomized, 86 completed the study
  - 9 patients discontinued due to COVID-19 lockdown, 1 due to closure of the assisted living facility
- At 2 hours post-dose (primary efficacy endpoint), a significant improvement from baseline in PEC total score was observed in the both the 40 ug and 60 µg groups compared with placebo (**Figure 2A and 2B**)

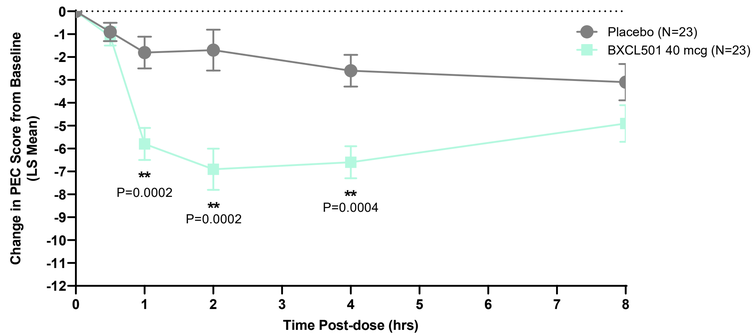
Figure 2A: Change in PEC Score ± SEM Over 8 Hours After Treatment Administration in Part A



Efficacy Results at 120 mins	PEC Total Score	Placebo	BXCL501 30 mcg	BXCL501 60 mcg
	Change from Baseline (LS Mean)	-3.0	-5.3	-7.1 **
	Response °	7%	25%	70% **

° Proportion achieving ≥ 40% PEC reduction. ** p-value <0.05; *** p-value < 0.001

Figure 2B: Change in PEC Score ± SEM Over 8 Hours After Treatment Administration in Part B



Efficacy Results at 120 mins	PEC Total Score	Placebo	BXCL501 40 mcg
	Change from Baseline (LS Mean)	-1.7	-6.9**
	Response °	9%	39%*

° Proportion achieving ≥ 40% PEC reduction. * p-value < 0.05 ** p-value < 0.001

- Other outcome measures also supported superiority of the 40 and 60 ug doses over placebo in this study (**Figures 3-5**)
- None of the patients received rescue medication during the study

Figure 3: Response Rates as Defined by CGI-I of 1 or 2 (very much improved or much improved)

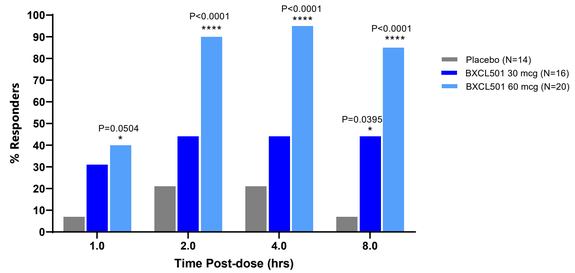


Figure 4: Change in PAS Score ± SEM Over 8 Hours After Treatment

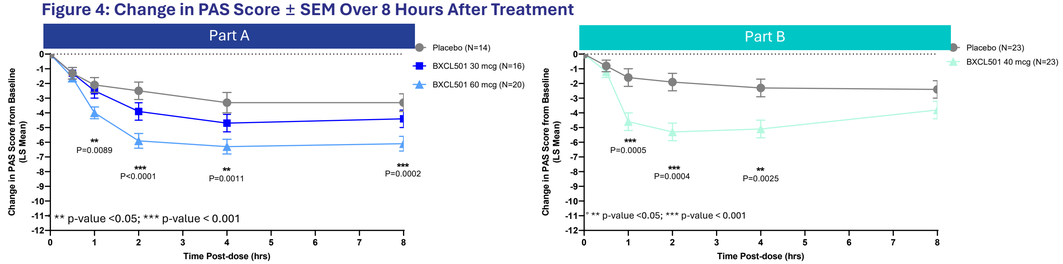
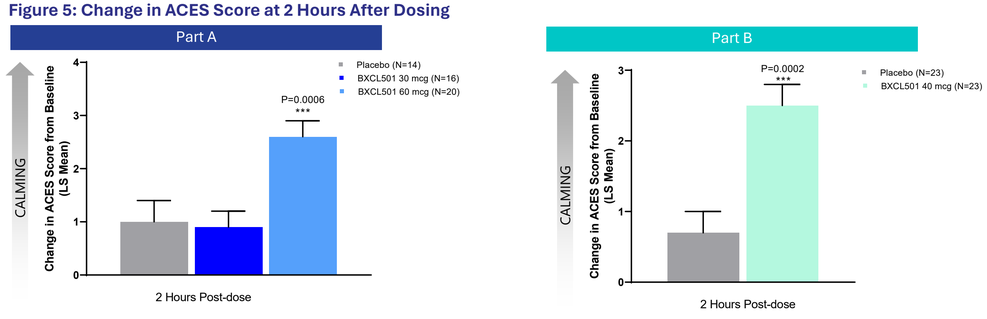


Figure 5: Change in ACES Score at 2 Hours After Dosing



- Overall, a total of 43 patients experienced at least 1 TEAE (**Table 2**).
- None of the TEAEs were considered severe or required medical intervention and no patients discontinued the study due to AEs
- No cases of syncope or falls were reported in any of the groups
- Total of 2 SAEs (sepsis and hypernatremia) were reported in 1 patient in the BXCL501 40 µg group on Day 2. Both SAEs were considered unlikely to be related to the study drug
- No clinically significant abnormal ECG changes observed in any patient at baseline or at 2 or 24 hours post-dose

Table 2: Adverse Events by Severity

AE	Severity	BXCL501 30 µg (N=16)	BXCL501 40 µg (N=23)	BXCL501 60 µg (N=20)	Placebo (N=37)
Somnolence	Mild	9 (56.3)	8 (34.8)	11 (55.0)	2 (5.4)
	Moderate	0	0	1 (5.0)	0
Dizziness	Mild	1 (6.3)	1 (4.3)	1 (5.0)	0
Headache	Mild	0	0	1 (5.0)	0
Hypotension	Mild	0	2 (8.7)	1 (5.0)	0
	Moderate	0	0	1 (5.0)	0
Orthostatic hypotension	Mild	0	0	1 (5.0)	0
	Moderate	1 (6.3)	0	0	0
Dry mouth	Mild	0	1 (4.3)	1 (5.0)	0
Nausea	Mild	0	1 (4.3)	1 (5.0)	0
Gastrooesophageal reflux disease	Moderate	0	1 (4.3)	0	0
Vomiting	Moderate	0	1 (4.3)	0	0
Dehydration	Mild	0	2 (8.7)	0	0
	Moderate	0	1 (4.3)	0	0
Hypernatraemia	Moderate	0	1 (4.3)	0	0
Bradycardia	Mild	0	0	1 (5.0)	0
Sepsis	Moderate	0	1 (4.3)	0	0
Urinary tract infection	Moderate	0	1 (4.3)	0	0

Summary

- ✓ **Results of the TRANQUILITY I study showed that statistically significant reductions in agitation were achieved with both 60 µg dose and 40 µg dose as measured by PEC, PAS, ACES, and CGI**
- ✓ **The study provided evidence that doses in the range of 30-60 µg of BXCL 501 seem to be safe and well tolerated and can be further characterized in future larger studies of patients with agitation associated with dementia**

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

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