A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF PRN DOSING OF BXCL501 OVER A 12 WEEK PERIOD IN SUBJECTS WITH AGITATION ASSOCIATED WITH DEMENTIA

NCT05271552

November 18, 2022

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF PRN DOSING OF BXCL501 OVER A 12 WEEK PERIOD IN SUBJECTS WITH AGITATION ASSOCIATED WITH DEMENTIA

PROTOCOL NUMBER:	BXCL501-303
STUDY PHASE:	Phase 3
IND NUMBER:	156685
PROTOCOL VERSION:	3.0
PROTOCOL DATE:	23Feb2022
AMENDMENT 1	20May2022
AMENDMENT 2:	18Nov2022
SPONSORED BY:	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 Phone: [redacted]

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Independent Ethics Committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of BioXcel Therapeutics, Inc.

PROTOCOL APPROVAL

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF PRN DOSING OF BXCL501 OVER A 12 WEEK PERIOD IN SUBJECTS WITH AGITATION ASSOCIATED WITH DEMENTIA

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SPONSOR: BioXcel Therapeutics, Inc.
555 Long Wharf Drive
12th Floor
New Haven, CT 06511
U.S.A.

STUDY PRODUCT: BXCL501

Sponsor Approval:

Date: 21-Nov-2022 Signature: DocuSigned by: [redacted]
Signer Name [redacted]
Signing Reason: I have reviewed this document
Signing Time: 21-Nov-2022 | 7:14:45 AM PST
252C5B3006CB434898D1752EACA46C70

[redacted] MD
Chief Medical Officer

1. PROCEDURES IN CASE OF EMERGENCY

Table 1.1: Sponsor/Contract Research Organization Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted] Pharm.D. Chief Executive Officer	Cognitive Research Corporation 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 Telephone: [redacted] Cell: [redacted]
Clinical Operations Leader	[redacted] MSHS Director, Clinical Projects	Cognitive Research Corporation 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 Telephone: [redacted] Cell: [redacted]
Medical Monitor/ 24-hour Emergency Contact	[redacted] MD	Cognitive Research Corporation 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 Cell: [redacted]
	Secondary Contact: [redacted] MD	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 Telephone: [redacted] Cell: [redacted]

2. INVESTIGATOR AGREEMENT

PROTOCOL TITLE: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY AND SAFETY STUDY OF BXCL501 FOR THE TREATMENT OF AGITATION ASSOCIATED WITH DEMENTIA

PROTOCOL NUMBER: BXCL501-303

I have read the protocol and agree that it, along with the related Clinical Trial Agreement, contains all the details necessary to carry out the study. I will conduct this study according to the protocol and will complete the study in the time agreed. Potential additions or modifications to the study will be by mutual written agreement between BioXcel Therapeutics, Inc. and me and will be documented and filed, if required, with the Institutional Review Board and the United States Food and Drug Administration.

I will provide copies of the protocol and other pertinent information to all individuals responsible for assisting me in the study.

BioXcel Therapeutics, Inc., Cognitive Research Corporation, and their designees will have access to source documentation from which case reports have been generated.

Investigator Signature: _____ Date: _____

Investigator Name (print): _____

3. SYNOPSIS

Name of sponsor/company: BioXcel Therapeutics, Inc.

Name of investigational product: BXCL501

Name of active ingredient: Dexmedetomidine (DEX)

Protocol number: BXCL501-303

Title of study: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF PRN DOSING OF BXCL501 OVER A 12 WEEK PERIOD IN SUBJECTS WITH AGITATION ASSOCIATED WITH DEMENTIA

Estimated number of study center(s): Multicenter, up to 30 sites in the United States (US)

Phase of development: Phase 3

Rationale:

Acute agitation is a severe, disruptive, and distressful complication of many chronic mental illnesses, including schizophrenia (Osser and Sigadel, 2001), bipolar disorder (Alderfer and Allen, 2003) and dementia (Conn and Lieff, 2001). Current standard of care treatment of an acute episode of agitation is pharmacological tranquilization with antipsychotics (either typical or atypical) and/or benzodiazepines (Currier and Trenton, 2002; Currier et al., 2004; Battaglia, 2005). These drugs are available in a variety of forms, including oral tablets, orally disintegrating tablets, oral liquids, and intramuscular injections (IM). Efficacy has been demonstrated for each of these agents, but some are characterized by slow onset of action, potentially prolonging the suffering of agitated patients and increasing the need for physical restraint or seclusion (Allen et al., 2003).

BXCL501, an orally dissolving film of dexmedetomidine, is designed as a self-administered, low-dose, sublingual film with mucoadhesive properties. It is expected that its administration in agitated patients will lead to a clinically meaningful reduction in agitation without excessive sedation or use of antipsychotics or intramuscular preparations. This study is designed to assess safety and efficacy of up to 28 doses of BXCL501 administered for the acute treatment of clinically significant agitation episodes over a study period of 12 weeks. When an episode of agitation occurs that meets dosing criteria, subjects may be dosed with BXCL501 40 µg or 60 µg doses. BXCL501 will be evaluated in male and female subjects, 65 years and older, who require minimal assistance with their activities of daily living (ADLs) and reside in a facility where such assistance is available. The clinical diagnosis of "probable Alzheimer's Disease (AD)" will be based on the 2018 National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria, which includes patient biomarker data as part of the research diagnosis (Jack et al., 2018). If patient biomarker data are unavailable, per the 2018 NIA-AA diagnostic criteria, the clinical diagnosis of probable AD will be based on the 2011 NIA-AA criteria (McKhann et al., 2011).

Objectives:

Primary objective:

To determine the safety and efficacy of BXCL501 dosing for episodes of agitation associated with dementia when they occur (given as needed [PRN]), for a maximum of 28 doses within a 12-week treatment period.

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Key Secondary objective:

- To determine the earliest time at which an effect on agitation is apparent, as measured by change from baseline in Positive and Negative Syndrome Scale – Excited Component (PEC) total score.

Study Design: This is a randomized, double-blind, placebo-controlled, parallel group, 3-arm study assessing efficacy, safety, and tolerability of two doses of BXCL501 in male and female subjects (65 years and older) with acute psychomotor agitation. BioXcel Therapeutics intends to conduct this study in subjects who have a diagnosis of probable AD based on NIA-AA criteria (2018) and explore the efficacy and safety of an "as needed" BXCL501 dosing regimen on agitation in these subjects. Subjects will be dosed PRN with a maximum of 28 doses over a 12-week period. Subjects may only be dosed once per day; Day 84 is the last day a subject may receive a dose of study drug. Once a subject has received 28 doses of BXCL501, they will continue to be followed for the remainder of the 12-week study period.

It is expected that not all episodes of agitation will be able to be assessed due to timing of the episodes and other factors. Every attempt will be made to capture and treat the majority of episodes.

Subjects will receive a single film consisting of BXCL501 40 µg dose or BXCL501 60 µg dose or placebo in a 1:1:1 randomization scheme. Randomization will be stratified based on antipsychotic use in the past month. Subjects must reside in a care facility where all study-related procedures and study drug dosing will be performed by trained research staff under the supervision of the Principal Investigator. The staff at the care facility will work in collaboration with the Principal Investigator/research staff relative to identifying potentially qualifying agitation episodes. The research staff will be responsible for assessing the agitation episode to determine eligibility and appropriateness to administer a dose of study drug.

At the time of dosing, subjects will be instructed on how to take the investigational product sublingually and be made aware that they should retain the investigational product in the sublingual until dissolved. The subject will self-administer under the supervision of a trained research staff member. Placement of the strip will be confirmed and documented. The oral cavity will be checked for irritation periodically after dosing and over the course of the study. Participants will be allowed fluids as desired at least 15 minutes after completion of dosing. If the subject is unable to self-administer and has not received drug, the event will be recorded, and the subject's participation will continue in order to ascertain the number of agitation episodes for which the subject was able to self-administer and the number of agitation episodes for which the subject was not able to self-administer.

Up to 1 hour prior to dosing, blood pressure (BP) and orthostatic BP will be collected only if possible. Every effort should be made to ensure the subject is well-hydrated prior to dosing. Research staff should remain with the subject for the first 2 hours after dosing as other assessments will need to be performed.

Safety, efficacy, and tolerability will be measured periodically throughout the treatment period according to the timepoints provided in the Schedule of Events tables (Table 3.1 and Table 3.2). All efforts should be made to complete all assessments as per protocol. Should the subject's status warrant it, standard of care rescue treatment for agitation may be initiated at any time, preferably after the 4-hour assessments are completed.

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Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or electrocardiogram (ECG) parameter taken during prescreening and deemed clinically significant by the investigator will be repeated. If the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be stable and no longer of clinical concern the subject can be randomized into the study.

Independent Data Monitoring Committee

This study will be monitored under the supervision of a Data Monitoring Committee (DMC) which is independent from the Sponsor. The DMC is comprised of externally based individuals with expertise in clinical research and biostatistics. The primary responsibilities of the DMC are to review and evaluate the safety data during the course of the study and make appropriate recommendations regarding the conduct of the clinical study to the Sponsor.

Number of subjects (planned): Approximately 150 subjects will participate in this study. This study will be conducted at up to 30 sites in the US.

Subjects: Eligible individuals with dementia associated with a diagnosis of probable AD or their legally authorized representative (LAR), will sign an informed consent form (ICF) before any study-related procedures are performed.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

1. Male and female subjects 65 years and older.
2. All subjects must have a diagnosis of probable Alzheimer's disease based on NIAAA criteria (2018). If patient biomarker data are unavailable, per the 2018 NIA-AA diagnostic criteria, the clinical diagnosis of probable AD will be based on the 2011 NIA-AA criteria.
3. Episodes of psychomotor agitation (e.g., kick, bite, flailing) to the point that it impairs social activities, requires staffing, or medical intervention, or impairs ability for functional activities of daily living should be observed if possible 2 weeks prior to Screening.
4. Subjects exhibit behaviors that are congruent with the International Psychogeriatric Association criterion for agitation representing a change from the subject's usual behavior.
5. Subjects who have a score of 15 to 23 on the Mini-Mental State Exam (MMSE) at Screening and at Pre-dose and require minimal assistance with activities of daily living (e.g., bathing, dressing, and toileting).
6. Subjects who read, understand, and provide written informed consent, or who have a LAR to provide consent on their behalf.
7. Subjects who are deemed to be medically appropriate for study participation by the principal investigator supported by a detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology, and urinalysis.
8. Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agree to use a medically acceptable and effective birth control method throughout the study and for one week following the end of the study. Medically acceptable methods of contraception that may be used by the

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participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include the rhythm method, withdrawal, condoms alone, or diaphragm.

9. Subjects who are at their current location for at least 14 days before Screening and plan to remain at the same location for the duration of the study.
10. Subjects must be able to self-administer the investigational product.
11. Subjects who are on a stable concomitant medications regimen for the treatment (including off-label agents for the prevention of agitation) of any concurrent conditions for at least 2 weeks prior to the Screening Visit.

Exclusion Criteria

1. Subjects with dementia or other memory impairment not due to probable AD, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia.
2. Clinical diagnosis of probable AD should not be applied when there is evidence of a cerebrovascular incident temporally related to the worsening of cognitive function.
3. Subjects with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription drugs during urine screening excludes the subject.
4. Subjects with significant risk of suicide or homicide per the investigator's assessment, or any patient with an answer of "yes" to item 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) must be excluded.
5. Subjects who have hydrocephalus, seizure disorder, or history of significant head trauma, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, or focal neurological findings, with a recent (1 year) large (non-microvascular) stroke who may be considered medically unstable or in recovery must be excluded.

   Note: Subjects with a remote (>5 years) history of stroke may be included, regardless of size/location.
6. Subjects with laboratory or ECG abnormalities (e.g., advanced heart block [second-degree or above atrioventricular block without pacemaker], diagnosis of sick sinus syndrome) considered clinically significant by the investigator or qualified designee and that would have clinical implications for the subject's participation in the study must be excluded.
7. Subjects with serious, unstable, or uncontrolled medical illnesses must be excluded. These include current moderate to severe hepatic impairment, or renal, gastro-enterologic, respiratory, cardiovascular (including ischemic heart disease, congestive heart failure), endocrinologic, or hematologic disease.
8. Subjects who have received an investigational drug within 30 days prior to Screening must be excluded.
9. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine or who are unable to use the sublingual film must be excluded, e.g., subjects with a history of allergic reactions to dexmedetomidine.

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10. Subjects whose agitation is attributed to pain or infection, concomitant medication, environmental conditions, or psychiatric condition other than dementia as determined by the investigator. 11. Subjects with any other condition, which in the judgment of the investigator would prevent them from entering or completing the study, such as recent clinical weight loss, chronic dehydration, or a recent clinically significant infection are excluded. 12. Subjects who are currently suffering from substance abuse. 13. Subjects who have had surgery within 30 days prior to Screening or scheduled surgery during the study period. 14. Subjects who are pregnant or breast feeding. 15. Patients with a potential cause for delirium (relatively recent onset agitation and dementia). Randomization criteria prior to dosing the first dose of study drug are: 1. Subjects must have a total score ≥14 points on the PEC scale 2. Subjects who are judged to be clinically agitated at pre-dose with a total score of ≥8 on the 4 items (aberrant vocalization, motor agitation, aggressiveness, and resisting care) comprising the Pittsburgh Agitation Scale (PAS). Criterion for dosing study drug for subsequent episodes of agitation: Subjects must have a total score ≥14 points on the PEC scale
Test Product, Dose, and Mode of Administration: BXCL501 will be provided as a thin, solid-dose film formulation of dexmedetomidine, approximately 286 mm^2 in area, designed to dissolve in the sublingual space. Dosing delivers 40 µg or 60 µg sublingually.
Reference therapy, dosage and mode of Administration: Matching placebo films to be taken sublingually as described above.
Duration of Treatment: A study period of 12 weeks with a maximum of 28 doses.

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Criteria for Evaluation:

Efficacy:

Primary Endpoint

The change from baseline in PEC total score at 2 hours post-dose for the first episode of agitation constitutes the primary endpoint for this study. The PEC comprises 5 items associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each scored 1 (minimum) to 7 (maximum). The PEC, the sum of these 5 subscales, thus ranges from 5 (absence of agitation) to 35 (extremely severe).

Key secondary efficacy endpoints

- PEC change from baseline at 1 hour post-dose of study treatment for the first episode of agitation (measures *initial* efficacy)
- PEC change from baseline at 30 minutes post-dose of study treatment for the first episode of agitation (measures *initial* efficacy)

Continued efficacy endpoints

A collection of endpoints will be considered as part of the continued efficacy analysis. These endpoints can be viewed as follows:

1. Those focusing on a single treated episode following the first treated episode of agitation which include the following:
   - PEC change from pre-dose at 2 hours post-dose of study treatment for the last treated episode of agitation, the second treated episode of agitation, and the third treated episode of agitation

2. Summary measures of efficacy across all administrations of BXCL501 which include the following:
   - average PEC change from pre-dose at 2 hours post-dose of study treatment over all episodes of agitation,
   - the percentage of all treated episodes of agitation satisfying the definition of PEC responder, an episode with at least a 40% reduction in PEC total score from pre-dose at 2 hours post dose of study treatment
   - frequency of all treated episodes of agitation, and
   - the percentage of all treated episodes of agitation for which the PEC change from pre-dose at 2 hours post-dose of study treatment is a reduction of at least 5 points

3. Multivariate outcomes of:
   - PEC change from pre-dose at 2 hours post-dose of study treatment for all episodes of agitation and
   - severity of agitation pre-dose for all episodes of agitation

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4. The comparison of efficacy at the last treated episode of agitation and the first treated episode of agitation.

Safety and tolerability assessments:

All observed and volunteered adverse events (AEs) will be recorded. Clinical laboratory tests, 12-lead electrocardiogram (ECG) with rhythm strip or if the subject is symptomatic (i.e., short of breath, dizzy), pulse oximetry, and vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate will be monitored periodically throughout the study unless the subject is symptomatic and warrants further evaluation at the discretion of the investigator.

Additional Assessments:

Demographics, Medical and Psychiatric History, Smoking History, Prior and Concomitant Medication, Physical Examination, PK, and Pregnancy.

Statistical Analysis:

Safety and Tolerability: Safety data analysis will be conducted on all subjects receiving at least 1 dose of study drug. The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment, relationship to study drug, and severity. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Listings of subjects who experience withdrawal due to an AE, serious AEs and/or death will be presented. Laboratory parameters will be summarized by treatment using descriptive statistics and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics.

Efficacy:

The null and alternative hypotheses to be tested for the primary endpoint are stated as H_{01}: $\Delta_{BXCL501\_60} = \Delta_{PBO}$ and H_{A1}: $\Delta_{BXCL501\_60} \neq \Delta_{PBO}$ and H_{02}: $\Delta_{BXCL501\_40} = \Delta_{PBO}$ and H_{A2}: $\Delta_{BXCL501\_40} \neq \Delta_{PBO}$, where $\Delta_{BXCL501\_60}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 60 µg group, $\Delta_{BXCL501\_40}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 40 µg group, and Δ_{PBO} denotes the change from baseline in the PEC at 2 hours post-dose in the placebo group. These hypotheses will be tested using a mixed model repeated measures (MMRM) model. To account for the testing of two hypotheses, the two-sided significance level for each test will be determined using the Bonferroni correction with each hypothesis tested at a significance level of 0.025.

The null and alternative hypotheses to be tested for the two key secondary endpoints are similar to those for the primary endpoint with the timepoint for testing being 1 hour post-dose for the first key secondary endpoint and 30 minutes post-dose for the second key secondary endpoint. These hypotheses will be tested using the MMRM model described for the primary analysis.

A variety of analysis approaches for the continued efficacy and other secondary endpoints will utilized depending on the outcome and will include MMRM and ANCOVA models and descriptive methods such as frequency distributions.

Details of the analyses to be conducted will be described in the statistical analysis plan (SAP) that will be finalized before database lock.

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Sample Size Determination: Approximately 150 subjects are anticipated to be enrolled. Assuming a standard deviation of 4 in change from baseline in the PEC at two hours post-dose and a two-sided two-sample t-test, enrollment of 150 subjects provides in excess of 90% power to detect a difference in mean PEC score of 2.9 units or more, at the 0.025 alpha-level (adjusted for multiplicity of doses) for either dose versus placebo. A blinded sample size recalculation is currently planned when approximately 50% of the PEC total score data are available. The pooled standard deviation of the change from baseline in PEC total score will be computed at each time point. The sample size will then be recalculated with the potential to adjust the sample size accordingly.

Table 3.1: Schedule of Events – Screening, Pre-Dose, and Post-Dose Assessments

Activity	Timepoints									
			Post Dose							
	Screening[1] (≤ 45 days)	Pre-dose[2] -90 min to time 0	30 min (+10 min)	1 hr (+15 min)	2 hr (+30 min)	4 hr (±1 hr)	*Optional*[3] 8 hr (±1 hr)	*Optional*[3] 12 hr (±1 hr)	Day 2[13] 24 hr (±2 hrs)	Day 3 (+1 day)
Informed consent	X									
Medical history	X									
Inclusion/Exclusion	X	X[4]								
Demographics	X									
Weight	X									X[5]
Height	X									
Mini-Mental State Exam	X	X[4]								X[5]
ADAS-Cog 12	X									X[5]
Physical exam	X									X[5]
Safety laboratory assessments[6,8]	X									X[5]
Urine pregnancy test	X									
UDS[7]	X									
UTI[8]	X									
Johns Hopkins Fall Risk Assessment	X									
ECG with rhythm strip[9]	X	X			X	X	X	X	X	X[5]
Pulse oximetry		X			X	X	X	X	X	
Resting vital signs[10]	X	X	X	X	X	X	X	X	X	X and X[5]
Orthostatic vital signs[11]	X	X		X	X	X	X		X	X and X[5]
Randomization		X[4]								
Agitation behaviors		X			X					
Study drug administration		X								
PAS	X	X[2]			X	X	X	X	X	

Activity	Timepoints									
			Post Dose							
	Screening[1] (≤ 45 days)	Pre-dose[2] -90 min to time 0	30 min (+10 min)	1 hr (+15 min)	2 hr (+30 min)	4 hr (±1 hr)	*Optional*[3] 8 hr (±1 hr)	*Optional*[3] 12 hr (±1 hr)	Day 2[13] 24 hr (±2 hrs)	Day 3 (+1 day)
PEC	X	X[2]	X	X	X	X	X	X	X	
ACES		X[2]		X	X	X	X	X	X	
CGI-Severity (agitation)	X	X[2]			X	X				
CGI-Improvement (change in agitation)			X	X	X	X	X	X	X	
C-SSRS	X									X[5]
Sublingual (SL) assessment		X	X		X	X			X	X[5]
PK sampling[12]		X		X	X	X	X			
Drug Likability Scales						X				
Likability Questionnaire						X				
Concomitant medications	X	X	X	X	X	X	X	X	X	X and X[5]
Adverse events			X	X	X	X	X	X	X	X and X[5]

Abbreviations: ACES = Agitation-Calmness Evaluation Scale; ADAS-Cog 12 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 12; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CLIA = Clinical Laboratory Improvement Amendments; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; hr = hour(s); min = minutes; MMSE = Mini-Mental State Exam; PAS = Pittsburgh Agitation Scale; PEC = Positive and Negative Syndrome Scale – Excited Component; PK = pharmacokinetic; SL = sublingual; UDS = urinary drug screen; UTI = urinary tract infection

Notes to the Schedule of Events:

[1] Screening assessments to be performed within 45 days before the first dose of study drug and may be conducted over more than one day. If a subject does not become agitated within the 45 day window, the subject is considered a screen failure. However, that subject can be rescreened once at the discretion of the investigator. Please note that some screening assessments do not need to be repeated if assessments were conducted on the day of dosing. All Screening and Pre-dose assessments should be completed before the study drug is administered. Antihypertensives or other medications may be held as per protocol on the day of study drug administration at the discretion of the investigator.

[2] Pre-dose assessments will have a window of 90 minutes prior to administration of study drug. If possible, PEC, PAS, ACEs, and CGI-S should be performed within 15 minutes prior to dosing. All post-dose efficacy assessments should be conducted prior to any other assessments at each time point.

[3] The 8 hour and 12 hour post-dose assessments are not to be performed if the subject is asleep for the night.

[4] Review of Inclusion and Exclusion criteria and administration of the MMSE, which is only performed before the first dose of study drug.

[5] Only complete if Day 83 or Day 84 is the last dose of study drug. For all other Day 3 visits, only concomitant medications, AEs, and orthostatic and resting vital signs are to be assessed.

[6] Safety laboratory assessments will include clinical chemistry, hematology, and urinalysis.

[7] UDS is required at Screening. UDS will be re-collected prior to dosing if more than 21 days have passed since the Screening visit. Urine drug screen will be analyzed by a central laboratory.

[8] In cases where repeat laboratory tests may be required to confirm eligibility prior to dosing, a local laboratory may be used to obtain repeat test results.

[9]12-lead ECGs at Pre-Dose need to be collected, but if unable to be acquired due to agitation it will not constitute a protocol deviation. ECGs collected following treatment are to be performed prior to PK sampling. Triplicate ECGs are to be obtained approximately 1-3 minutes apart.

[10]Resting vital signs (SBP, DBP and HR) will be taken upon having the subject recumbent for 5 min at Screening, at Pre-Dose, and at 1, 2, and 4 hours post-dose. Triplicate measurements to be performed in case of SBP <90 mmHg, DBP <60 mmHg or pulse <60 bpm. Vital signs are to be done prior to drawing PK blood samples.

[11]Orthostatic measurements (SBP, DBP, HR) will be taken upon having the subject stand, with measurements taken upon standing after 1, 3, and 5 minutes, per Centers for Disease Control and Prevention guidelines for elderly at Screening, at Pre-dose, and at 1, 2, 4, 8, and 24 (Day 2) hours post-dose, and on Day 3 post-dose. A change from supine to standing of 20 mmHg SBP or 10 mmHg DBP must be repeated. If any one of the three orthostatic BP readings (1, 3 and/or 5 mins) show a decrease, from supine to standing, of 20 mmHg SBP or 10 mmHg DBP, the entire process will be repeated, which includes repeat resting and orthostatic BPs. Temperature and respiratory rate will be recorded when orthostatic measurement is indicated and are not required to be measured at resting vital sign timepoints. Vital signs are to be done prior to drawing PK blood samples.

[12]PK blood samples are to be collected at timepoints including pre-dose, and 1, 2, 4 and 8 hours after the first dose and fifth dose of study drug only. However, if the investigator documents it is not appropriate to collect a sample from the subject (e.g., inability to access a venous site to collect a blood sample due to psychomotor agitation, subject refusal, subject's current physical condition) at any of the scheduled timepoints, this will not result in the ineligibility of the subject's participation, should not result in early termination nor will this be considered a protocol deviation. All PK collections will have a window of ± 10 minutes. All PK sampling will occur only after all other assessments at that timepoint are conducted.

[13]Refer to Section 11.3 and Appendix 1 when Day2/24 hr and predose visits occur on the same day.

Table 3.2: Schedule of Events – Weekly Assessments

Activity	Timepoint[1]											
	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84 (EOS)[1]/ET
ECG with rhythm strip[2]	X		X		X		X		X		X	X
Resting vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic vital signs[4]	X		X		X		X		X		X	X
ADAS-Cog 12 Living												X
MMSE				X								X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (including body weight)				X				X				X
Safety laboratory assessments	X		X		X		X		X		X	X
Sublingual (SL) assessment	X		X		X		X		X		X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADAS-Cog 12 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 12; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; MMSE = Mini-Mental State Exam; SL = sublingual

Notes to the Schedule of Events:

[1] All visits have a window of ± 2 days. If a dose is administered on the same day or within the window of a scheduled weekly assessment, all dosing assessments as noted in Table 3.1 will be performed in lieu of the scheduled weekly assessment. If a 24 hour post-dose assessment coincides with a weekly assessment, then the post-dose 24 hour assessment will take precedence. Safety laboratory assessments should be conducted if they are scheduled as part of the weekly visit even though they are not part of the 24 hour post-dose assessments.

[2] If unable to be acquire an ECG due to agitation it will not constitute a protocol deviation. Triplicate ECGs are to be obtained approximately 1-3 minutes apart.

[3] Resting vital signs (SBP, DBP and HR) will be taken upon having the subject recumbent for 5 minutes. Triplicate measurements to be performed in case of SBP <90 mmHg, DBP <60 mmHg, or pulse <60 bpm. Vital signs are to be measured prior to drawing PK blood samples.

[4] Orthostatic measurements (SBP, DBP, HR) will be taken upon having the subject stand, with measurements taken upon standing after 1, 3, and 5 minutes, per Centers for Disease Control and Prevention guidelines for elderly. A change from supine to standing of 20 mmHg SBP or 10 mmHg DBP must be repeated. If any one of the three orthostatic BP readings (1, 3 and/or 5 mins) show a decrease, from supine to standing, of 20 mmHg SBP or 10 mmHg DBP, the entire process needs to be repeated, which includes repeat resting and orthostatic BPs. Temperature and respiratory rate will be recorded when orthostatic measurement is indicated and are not required to be measured at resting vital sign timepoints.

4. TABLE OF CONTENTS

4.1. List of Tables

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AD	Alzheimer's Disease
ADAS-Cog 12	Alzheimer's Disease Assessment Scale cognitive subscale
ADL	Activities of daily living
ADWG	Agitation Definition Work Group
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration vs time curve
BP	Blood pressure
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HR	Heart rate
hr	Hour
ICH	International Council for Harmonisation
IM	Intramuscular
IPA	International Psychogeriatric Association
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
kg	Kilogram
K_2EDTA	dipotassium ethylenediaminetetraacetic acid

Abbreviation	Definition
LAR	Legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minutes
mL	Milliliter
mmHg	Millimeters of mercury
MMSE	Mini-Mental State Exam
NIA-AA	National Institute on Aging and Alzheimer's Association
PANSS-PEC	Positive and Negative Syndrome Scale – Excited Component
PAS	Pittsburgh Agitation Scale
PK	Pharmacokinetic
PRN	As needed (pro re nata)
RASS	Richmond Agitation Sedation Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SL	Sublingual
TEAE	Treatment-emergent adverse event
µg	Microgram
UDS	Urine drug screen
US	United States
UTI	Urinary tract infection

6. INTRODUCTION

6.1. Background and Rationale

Acute agitation is a severe, disruptive, and distressful complication of many chronic mental illnesses, including schizophrenia (Osser and Sigadel, 2001), bipolar disorder (Alderfer and Allen, 2003) and dementia (Conn and Lieff, 2001). Current standard of care treatment of an acute episode of agitation is pharmacological tranquilization with antipsychotics (either typical or atypical) and/or benzodiazepines (Currier and Trenton, 2002; Currier et al., 2004; Battaglia, 2005). These drugs are available in a variety of forms, including oral tablets, orally-disintegrating tablets, oral liquids, and intramuscular injections (IM). Efficacy has been demonstrated for each of these agents, but some are characterized by slow onset of action, potentially prolonging the suffering of agitated patients and increasing the need for physical restraint or seclusion (Allen et al., 2003).

BXCL501, an orally dissolving film of dexmedetomidine, is designed as a self-administered, low-dose, sublingual film with mucoadhesive properties. It is expected that its administration in agitated patients will lead to a clinically-meaningful reduction in agitation without excessive sedation or use of antipsychotics or intramuscular preparations. This study is designed to assess safety and efficacy of up to 28 doses of BXCL501 administered for the acute treatment of clinically significant agitation episodes over a study period of 12 weeks. When an episode of agitation occurs that meets dosing criteria, subjects may be dosed with BXCL501 40 µg or 60 µg doses, or placebo. BXCL501 will be evaluated in male and female subjects, 65 years and older, who require minimal supervision or minimal assistance with their ADLs and reside in a facility where such assistance is available. Subjects who meet the criteria for a diagnosis of probable Alzheimer's Disease (AD) are eligible for the study. The criteria for probable AD are provided in McKhann et al, 2011).

6.2. Description of BXCL501

BXCL501 is a sublingual film comprised of dexmedetomidine, the active pharmaceutical ingredient and the following inactive ingredients: polyethylene oxide, hydroxypropyl cellulose, sucralose, peppermint oil, Emerald Green colorant, and Food, Drug, and Cosmetic Act Blue #1 colorant.

No special transport or storage conditions are required for BXCL501. Packaged films can be stored at room temperature (25°Celsius) and ambient humidity.

6.3. Non-Clinical Pharmacology

6.3.1. Pharmacodynamics

Medetomidine is a racemic mixture of 2 stereoisomers: dexmedetomidine and levomedetomidine. The active isomer is dexmedetomidine, whereas the other isomer, levomedetomidine, is non-active. Dexmedetomidine is a highly selective α_2 adrenoceptor agonist on presynaptic neurons. The stimulation of these receptors leads to a decrease in norepinephrine release from presynaptic neurons with inhibition of postsynaptic activation, which attenuates CNS arousal, especially in the locus coeruleus of the brain (MHRA, 2014).

Since the pharmacologic effects of IV dexmedetomidine have been characterized, BioXcel sought to evaluate various dexmedetomidine metrics following administration by the sublingual (SL) route. BioXcel Therapeutics, Inc. conducted 3 nonclinical studies to evaluate the pharmacodynamics of different BXCL501 formulations as compared to dexmedetomidine administered by different routes, including sublingual liquid administration.

Overall, the studies demonstrated that sublingual administration in animal models produce sufficient exposure to elicit a calming effect in a rat model of aggressive behavior (intruder model).

6.4. Clinical Experience and Pharmacokinetics

6.4.1. Phase 3 Study BXCL501-301

Study BXCL501-301 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 in agitation associated with schizophrenia with 3 dosing groups (BXCL501 120 µg, BXCL501 180 µg, and placebo). The study was conducted at 15 investigative sites in the United States.

Male and female patients, between the ages of 18 to 75 years, who had met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for schizophrenia, schizoaffective, or schizophreniform disorder were eligible for the study.

The primary objective of this study was to determine if a single dose of BXCL501 effectively reduces symptoms of acute agitation associated with schizophrenia, schizoaffective disorder or schizophreniform disorder. The primary efficacy endpoint was mean change from baseline in PEC total score at 2 hours following the administration of BXCL501 180 µg and BXCL501 120 µg, compared to placebo.

A total of 380 subjects were enrolled in the study. Of these subjects, all received 1 or more doses of investigational product: 125 (BXCL501 180 µg), 129 (BXCL501 120 µg), and 126 (placebo).

The results of this study demonstrated that a single sublingual dose of BXCL501 at 180 µg or 120 µg effectively reduced the severity of agitation in subjects with schizophrenia, schizoaffective, or schizophreniform disorder. The treatment produced a rapid calming effect.

In this study, the primary efficacy endpoint was met in both BXCL501 treatment groups. At 2 hours post-dose, significant improvements (ie, decreases) from baseline in PEC total scores were observed in the BXCL501 180 µg and BXCL501 120 µg treatment groups compared to placebo. Mean changes from baseline were -10.4 points and -8.4, respectively, versus -4.7 for placebo. LSM differences from placebo were -5.5 ($P < 0.0001$) and -3.7 ($P < 0.0001$) for the 180 µg and 120 µg BXCL501 treatment groups, respectively.

The secondary efficacy endpoint (ie, the earliest time where an effect on agitation was apparent) was also met. As early onset of action is an important attribute for therapy in reducing agitation, the BXCL501 180 µg group showed a statistically significant separation from placebo as early as 20 minutes post dosing (LS mean difference of -1.2 [$P = 0.0032$]), and at 30 minutes post-dose the LS mean difference was clinically meaningful (-2.4, $P < 0.0001$). Continuous improvements were demonstrated from 30 minutes with a peak effect at 2 hours post-dosing. Statistically significant separation from placebo for the BXCL501 120 µg group occurred at 30 minutes post-dose (LS mean difference of -1.3 [$P = 0.0075$]) and at 45 minutes post-dose the LS mean

difference was clinically meaningful (-2.1, P <0.0001). Continuous improvements from that point forward were observed with a peak effect also at 2 hours post-dosing.

All exploratory endpoints (ie, PEC responders, CGI-I, CGI-I responders, Agitation-Calmness Evaluation Scale [ACES], and PANSS total score) supported the efficacy of BXCL501 in reducing agitation.

The safety data collected in this study showed that BXCL501 at 180 µg and 120 µg was generally well tolerated and had a favorable safety profile in the treatment of subjects with agitation. The TEAEs reported in this study were consistent with known common side effects of dexmedetomidine, namely dry mouth, bradycardia, hypotension, and somnolence. A higher proportion of subjects in the BXCL501 120 µg and 180 µg groups experienced TEAEs of somnolence compared with placebo-treated subjects. Most events of somnolence were considered to be mild in severity; none were considered to be severe. It is important to note that there were no cases of syncope or falls reported in this study.

6.4.2. Phase 3 Study BXCL501-302

Study BXCL501-302 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 in agitation associated with bipolar disorder with 3 dosing groups (BXCL501 120 µg, BXCL501 180 µg, and placebo). The study was conducted at 15 investigative sites in the United States.

Male and female patients, between the ages of 18 to 75 years, who had met DSM-5 criteria for bipolar I or bipolar II disorder were eligible for the study.

A total of 380 subjects were enrolled in the study. Of these subjects, 378 received 1 or more doses of study drug and comprised the Safety Population (126 subjects each in the BXCL501 180 µg, BXCL501 120 µg, and placebo groups).

The results of this study demonstrated that a single sublingual dose of BXCL501 at 180 µg or 120 µg effectively reduced the severity of agitation in subjects with bipolar I or II disorder as compared to placebo. The treatment produced a rapid calming effect.

In this study, the primary efficacy endpoint was met in both BXCL501 treatment groups. At 2 hours post-dose, significant improvements (ie, decreases) from baseline in PEC total scores were observed in the BXCL501 180 µg and BXCL501 120 µg treatment groups compared with placebo. Mean changes from baseline at 2 hours post-dose were -10.4 and -9.0 points, respectively, versus -4.9 for placebo; LSM mean differences from placebo were -5.4 (P< 0.0001) and -4.1 (P < 0.0001) for the BXCL501 180 µg and 120 µg groups, respectively.

Significant and clinically meaningful improvements from baseline in PEC total scores were maintained at 4, 6, and 8 hours post-dose in the BXCL501 180 µg group with mean changes of -10.6, -9.9, and -9.1, respectively, with P < 0.0001 for all timepoints. The same pattern was observed in the BXCL501 120 µg dose group with mean changes of -9.5, -9.2, and -8.5, respectively, with P < 0.0001 for all timepoints.

As rapid onset of action is an important attribute for therapy in reducing agitation, the BXCL501 180 µg group showed a statistically significant separation from placebo at 20 minutes post-dose (LSM difference of -1.1 [P = 0.0070]). At 30 minutes post-dose a statistically significant improvement was also observed (LS mean difference of -1.7 [P = 0.0006]) with a peak efficacy

effect at 2 hours post dose (LSM difference of -5.4 [P < 0.0001]). Statistically significant separation from placebo for the BXCL501 120 μg group occurred at 20 minutes post dose (LSM difference of -1.0 [P = 0.0092]) and continuous improvements were evident from that point forward with a peak effect also at 2 hours post-dose (LSM difference of -4.1 [P < 0.0001]).

All exploratory endpoints (ie, PEC responders, CGI-I, CGI-I responders, ACES, and Young Mania Rating Scale) supported the efficacy of BXCL501 in reducing agitation.

Changes in secondary efficacy measures (ie, CGI-I and ACES scores) at 2 hours post-dose were consistent with the results for PEC total scores and were indicative of improvement in symptoms of agitation after treatment with BXCL501.

The safety data collected in this study showed that BXCL501 was generally well tolerated and had a favorable safety profile in the treatment of subjects with agitation. The TEAEs reported in this study were consistent with known common side effects of dexmedetomidine, namely dry mouth, bradycardia, hypotension, and somnolence. A higher proportion of subjects in the BXCL501 120 μg, and 180 μg groups experienced TEAEs of somnolence compared with placebo-treated subjects. Most events of somnolence were considered to be mild in severity, and none were considered to be severe. It is important to note that there were no cases of syncope or falls reported in this study.

6.4.3. Intravenous Study in Alzheimer's Disease (Study CRLIV091834)

BioXcel conducted a study to determine the safety and tolerability of intravenous (IV) dexmedetomidine in a geriatric population (Study CRLIV091834). This was a randomized, blinded, prospective, placebo controlled, parallel design, single center, investigator-initiated study conducted to evaluate the efficacy and safety of dexmedetomidine in the agitated subjects with mild probable Alzheimer's Disease (treatment allocation 5:2).

Subjects were male and female ranging from 55 to 75 years (both inclusive) of age with known cases of Mild Probable Alzheimer's Disease in accordance with the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for diagnosis of Alzheimer's Disease with a MMSE score between 20 – 24. A total of 14 subjects meeting the eligibility criteria as per protocol were randomized in the study, 10 subjects received dexmedetomidine IV infusion and 4 subjects received placebo treatment.

The primary endpoint was to determine the optimal IV dose and safety of dexmedetomidine in the target population by achieving calmness (Richmond Agitation Sedation Scale score [RASS] of -1 (Drowsiness, not fully alert easily awakened to voice, able to converse). Other objectives included how long the calming effect persists after discontinuation of study drug administration and to determine whether neurological effects like cognitive functioning, alertness/awareness, balance, and reaction time persist after drowsiness has resolved. The study also determined whether there were any adverse effects on blood pressure, heart rate, or respiration.

The initial dose of dexmedetomidine was 0.1 μg/kg/hour, with no loading dose with the desired endpoint being the attainment of easily arousable drowsiness (RASS -1) which can be reversed temporarily by verbal stimulation. Once the participant was drowsy but able to respond to verbal stimulation, the infusion was stopped, and time was recorded. The infusion was continued for up to 2.5 hours up to the maximum dose.

Results demonstrated that 7 out of 10 subjects achieved a RASS score of -1 with dexmedetomidine IV infusion, while only 1 out of 4 subjects achieved a RASS score of -1 with placebo IV infusion. The study demonstrated that dexmedetomidine IV infusion is effective in reducing agitation in the subjects with mild probable Alzheimer's Disease. It was safe and well tolerated without any clinically adverse effects on blood pressure and/or heart rate.

6.4.4. Phase 1b/2 Study BXCL501-103

Study BXCL501-103 was an adaptive Phase 1b/2 study design. It was a randomized, double-blind, placebo-controlled, multiple ascending dose study assessing efficacy, PK, safety, and tolerability of BXCL501 dosing in adult (65 years and older) males and females with acute agitation associated with dementia who were in an assisted living facility. The study was conducted at 4 investigative sites in the United States.

The study was designed to characterize a safe and tolerable dose range that would result in a calming effect as measured using the Pittsburgh Agitation Scale (PAS) by evaluating at least 10 subjects (4:1 randomization to BXCL501:placebo) at each of the 3 BXCL501 dose levels (30 µg, 60 µg, and 90 µg).

The primary objective of the study was to describe the safety and tolerability of single doses of BXCL501 for study of efficacy in treatment of acute agitation associated with dementia. The primary efficacy endpoint was mean change from baseline in PEC total score at 2 hours following the administration of BXCL501 30 µg, 60 µg, and 90 µg, compared to placebo.

A total of 54 subjects were enrolled and randomized: 16 (BXCL501 30 µg), 20 (BXCL501 60 µg), 4 (BXCL501 90 µg), and 14 (placebo); 54 subjects were in the Safety Population and 50 subjects were in the ITT population. All subjects completed the study.

When a blinded safety review of data from the 3 cohorts (BXCL501 30 µg, 60 µg, and 90 µg) suggested a potential dose-related increase in transient, reversible, known, expected and well-described adverse events the sponsor decided not to pursue the BXCL501 90 µg dose. Given that the subjects in this study are elderly, generally frail and suffer from dementia and out of an abundance of caution the sponsor decided not to pursue the BXCL501 90 µg dose. Thus, the safety assessment was focused on the BXCL501 30 µg and 60 µg treatment groups.

Please note that the 4 subjects who received BXCL501 90 µg were not included in the ITT population for the efficacy analysis; they were included in the Safety Population.

Efficacy

In the ITT Group (N=50), mean (SD) baseline PEC total score was 16.6 (3.5) in the BXCL501 60 µg, 18.3 (1.5) in the BXCL501 30 µg group, and 16.6 (2.7) in the placebo group. These scores indicate that most subjects had moderate agitation at baseline.

The primary efficacy endpoint was met in both BXCL501 treatment groups. At 2 hours post-dose, significant improvements (ie, decreases) from baseline in PEC total scores were observed in the BXCL501 60 µg and BXCL501 30 µg treatment groups compared to placebo. Mean changes from baseline were -7.1 points and -5.7, respectively, versus -2.5 for placebo. LSM differences from placebo were -4.6 ($P = 0.0002$) and -3.2 ($P = 0.0149$) for the BXCL501 60 µg and 30 µg treatment groups, respectively.

Significant and clinically meaningful improvements from baseline in PEC total scores were also observed at 1, 4, and 8 hours post-dose in the BXCL501 60 µg group with LS mean changes of -5.5, -8.3 and -9.3, respectively, with *P* values of 0.0006, 0.0004, and <0.0001, respectively.

For the BXCL501 30 µg dose group, a significant and clinically meaningful improvements from baseline in PEC total score were also observed at 30 minutes post-dose and at 4 hours post-dose with LS mean changes of -2.1 (*P* = 0.0295) and -6.8 (*P* = 0.0216), respectively.

Subjects who had a ≥40% decrease from baseline in PEC total score after dosing were considered to be treatment responders. At 2 hours post-dose, response rates in the BXCL501 60 µg and 30 µg dose groups were significantly higher (70.0% [*P* < 0.0001]) and 31.0% [*P* = 0.0447], respectively, compared with placebo [0%]).

Mean PAS total scores at baseline across the treatment groups ranged from 8.7 to 9.1 (PAS total scores can range from 0 to 16). At 2 hours post-dose, mean PAS total score was 3.3 in the BXCL501 60 µg group and 4.8 in the BXCL501 30 µg group. LS mean changes from baseline were -5.9 (P<0.0001) in the BXCL501 60 µg and -4.1 (P=0.0195) in the BXCL501 30 µg group. These changes indicated clinically meaningful improvements in agitation. Significant and clinically meaningful improvements in agitation were also observed at 1, 4, and 8 hours post-dose in the BXCL501 60 µg group with LS mean changes of -4.0, -6.3 and -6.1, respectively, with *P* values of 0.0017, 0.0004, and 0.0004, respectively.

Agitation was significantly reduced in the BXCL501 treatment groups compared with placebo based on the Modified Cohen-Mansfield Agitation Inventory. LS mean reduction in the Modified Cohen-Mansfield Agitation Inventory total score from baseline to 2 hours post-dose was -14.0 points (*P*<0.0001) in the BXCL501 60 µg group, -8.2 points in the BXCL501 30 µg group (*P* = 0.0364), compared with -2.9 points in the placebo group.

Mean ACES scores at baseline across the treatment groups ranged from 1.8 to 2.1 which indicated “moderate agitation” (score of 2). Significant increases in calming effect were observed in the BXCL501 60 µg group with LS mean changes from baseline of +1.1 (*P* = 0.0075) at 1 hour post-dose and +2.6 (*P* = 0.0004]) at 2 hours post-dose. These significant increases in calming effect were also observed at 4 hours and 8 hours post-dose (+2.7 [*P* <0.0001] and +2.2 [*P* <0.0001], respectively). In the BXCL501 30 µg group numerical increases in ACES score were observed at 1, 2, 4, and 8 hours post-dose, however, none of the increases were statistically significant compared with placebo.

Safety

When a blinded safety review of data from the 3 cohorts (BXCL501 30 µg, 60 µg, and 90 µg) suggested a potential dose-related increase in transient, reversible, known, expected and well-described adverse events, the sponsor decided not to pursue the BXCL501 90 µg dose. Given that the subjects in this study are elderly, generally frail and suffer from dementia and out of an abundance of caution the sponsor decided not to pursue the BXCL501 90 µg dose.

The proportion of subjects who experienced TEAEs was similar in the BXCL501 30 µg and 60 µg groups (68.8% and 70.0%, respectively) and higher (100%) in the BXCL501 90 µg group; no subject in the placebo group reported a TEAE. None of the subjects experienced a TEAE that was considered to be severe in intensity. There were no SAEs or deaths reported and no subject in any of the treatment groups discontinued (ie, withdrew) from the study due to an AE.

The TEAEs reported in this study were consistent with known common side effects of dexmedetomidine, namely dry mouth, bradycardia, hypotension, and somnolence.

The most frequently reported TEAE in the BXCL501 30 µg, 60 µg, and 90 µg treatment groups was somnolence (56.3% [n=9], 60.0% [n=12], and 75.0% [n=3], respectively); placebo was 0%. All cases of somnolence were considered by the investigator to be mild in severity, with the exception of 1 subject (103-01-037) in the BXCL501 60 µg cohort whose case was considered to be moderate in severity and not serious.

Hypotension was reported in only 3 subjects, of which 2 subjects were in the BXCL501 60 µg group (severity was mild in 1 subject and moderate in the other subject) and 1 subject was in the BXCL501 90 µg group (severity was mild).

A total of 5 subjects experienced TEAEs of orthostatic hypotension: 3 (75.0%) subjects in the BXCL501 90 µg group (all mild in severity), 1 (6.3%) subject in BXCL501 30 µg group (moderate in severity), and 1 (5.0%) subject in the BXCL501 60 µg group (mild in severity).

No cases of syncope or falls were reported in this study.

The Sponsor is exploring a BXCL501 40 µg dose in an extension of this study.

7. OBJECTIVES

7.1. Primary Objective

To determine the safety and efficacy of BXCL501 dosing for episodes of agitation associated with dementia when they occur (given as needed [PRN]), for a maximum of 28 doses within a 12 week treatment period.

7.2. Key Secondary Objective

To determine the earliest time at which an effect on agitation is apparent, as measured by change from baseline in Positive and Negative Syndrome Scale – Excited Component (PEC) total score.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, parallel group, 3-arm study assessing efficacy, safety, and tolerability of two doses of BXCL501 in male and female subjects (65 years and older) with acute psychomotor agitation. BioXcel Therapeutics intends to conduct this study in subjects who have a diagnosis of probable AD dementia based on NIA-AA criteria (2018) and explore the efficacy and safety of an "as needed" BXCL501 dosing regimen on agitation in these subjects. Prior to screening, subjects will be monitored by the research staff for frequency and characterization of agitation episodes for a period of 2 weeks to establish a baseline of frequency. Subjects will be dosed PRN with a maximum of 28 doses over a 12-week period. Subjects may only be dosed once per day; Day 84 is the last day a subject may receive a dose of study drug. Once a subject has received 28 doses of BXCL501, they will continue to be followed for the remainder of the 12-week study period. Day 84 is the last day that a subject can receive a dose of study drug. It is expected that not all episodes of agitation will be able to be assessed due to timing of the episodes and other factors. Every attempt will be made to capture and treat the majority of episodes. Subjects will receive a single film consisting of BXCL501 40 µg dose or BXCL501 60 µg dose or placebo in a 1:1:1 randomization scheme. Randomization will be stratified based on antipsychotic use in the past month. Subjects must reside in a care facility where all study-related procedures and study drug dosing will be performed by trained research staff under the supervision of the Principal Investigator. The staff at the care facility will work in collaboration with the Principal Investigator/research staff to identify potentially qualifying agitation episodes. The research staff will be responsible for assessing the agitation episode to determine eligibility and appropriateness to administer a dose of study drug.

At the time of dosing, subjects will be instructed on how to take the investigational product sublingually and be made aware that they should retain the investigational product in the sublingual until dissolved. The subject will self-administer under the supervision of a trained research staff member. Placement of the strip will be confirmed and documented. The oral cavity will be checked for irritation periodically after dosing and over the course of the study. Participants will be allowed fluids as desired at least 15 minutes after completion of dosing. If the subject is unable to self-administer and has not received drug, the event will be recorded, and the subject's participation will continue in order to ascertain the number of agitation episodes for which the subject was able to self-administer and the number of agitation episodes for which the subject was not able to self-administer.

Up to 1 hour prior to dosing, blood pressure (BP) and orthostatic BP will be collected only if possible. Every effort should be made to ensure the subject is well-hydrated prior to dosing. Research staff should remain with the subject for the first 2 hours after dosing as other assessments will need to be performed.

Safety, efficacy, and tolerability will be measured periodically throughout the treatment period according to the timepoints provided in the Schedule of Events tables (Table 3.1 and Table 3.2). All efforts should be made to complete all assessments as per protocol. Should the subject's status warrant it, standard of care rescue treatment for agitation may be initiated at any time, preferably after the 4-hour assessments are completed.

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter taken during Screening and deemed clinically significant by the investigator will be repeated. If the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be stable and no longer of clinical concern the subject can be randomized into the study.

8.2. Independent Data Monitoring Committee

This study will be monitored under the supervision of a Data Monitoring Committee (DMC) which is independent from the Sponsor. The DMC is comprised of externally based individuals with expertise in clinical research and biostatistics. The primary responsibilities of the DMC are to review and evaluate the safety data during the course of the study and make appropriate recommendations regarding the conduct of the clinical study to the Sponsor.

The DMC structure, roles and responsibilities, procedures, and safety data to be reviewed by the DMC are described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner, the recommendations of the DMC in terms of study continuation with or without alterations or of potential study termination.

The DMC meetings will occur as outlined in the DMC Charter, but can be convened at any time at the discretion of the DMC chair or the study medical officer. The DMC chair will be notified by the study medical officer of all SAEs and will receive summaries of other safety data as available.

The responsibilities of the DMC include:

- Evaluating the progress of the study, subjects' risk versus benefit, and other factors that could affect the study outcome
- Considering relevant information that may have an impact on the safety of the participants or the ethics of the study

The DMC Charter will be provided upon request.

8.3. Study Sites

The study will be conducted at up to 30 sites in the US.

9. SUBJECT POPULATION

9.1. Selection of Study Population

Individuals with probable AD dementia are eligible for enrollment in this study. Subjects must require at least minimal assistance with activities of daily living (e.g., bathing, dressing and toileting) and reside in a facility where such assistance is available. Most subjects enrolled in the study are expected to be ambulatory. A maximum of 15 non-ambulatory subjects representing ~10% of the total number of subjects will be enrolled. Subjects, or their LAR if necessary, will sign an ICF before any study-related procedures are performed.

9.1.1. Inclusion Criteria

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. Male and female subjects 65 years and older.
2. All subjects must have a diagnosis of probable Alzheimer's disease based on NIA-AA criteria (2018). If patient biomarker data are unavailable, per the 2018 NIA-AA diagnostic criteria, the clinical diagnosis of probable AD will be based on the 2011 NIA-AA criteria.
3. Episodes of psychomotor agitation (e.g., kick, bite, flailing) to the point that it impairs social activities, requires staffing, or medical intervention, or impairs ability for functional activities of daily living should be observed if possible 2 weeks prior to Screening.
4. Subjects exhibit behaviors that are congruent with the International Psychogeriatric Association criterion for agitation representing a change from the subject's usual behavior.
5. Subjects who have a score of 15 to 23 on the Mini-Mental State Exam (MMSE) at Screening and at Pre-dose and require at least minimal assistance with activities of daily living (e.g., bathing, dressing, and toileting).
6. Subjects who read, understand, and provide written informed consent, or who have a LAR to provide consent on their behalf.
7. Subjects who are deemed to be medically appropriate for study participation by the principal investigator supported by a detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology, and urinalysis.
8. Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agree to use a medically acceptable and effective birth control method throughout the study and for one week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include the rhythm method, withdrawal, condoms alone, or diaphragm.
9. Subjects who are at their current location for at least 14 days before Screening and plan to remain at the same location for the duration of the study.
10. Subjects must be able to self-administer study drug.

11. Subjects who are on a stable concomitant medications regimen for the treatment (including off-label agents for the prevention of agitation) of any concurrent conditions for at least 2 weeks prior to the Screening Visit.

9.1.2. Exclusion Criteria

A subject will be excluded from the study for any of the following reasons:

1. Subjects with dementia or other memory impairment not due to probable AD, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia.
2. Clinical diagnosis of probable AD should not be applied when there is evidence of a cerebrovascular incident temporally related to the worsening of cognitive function.
3. Subjects with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription drugs during urine screening excludes the subject.
4. Subjects with significant risk of suicide or homicide per the investigator's assessment, or any patient with an answer of "yes" to item 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) must be excluded.
5. Subjects who have hydrocephalus, seizure disorder, or history of significant head trauma, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, or focal neurological findings, with a recent (1 year) large (non-microvascular) stroke who may be considered medically unstable or in recovery must be excluded.

   Note: Subjects with a remote (>5 years) history of stroke may be included, regardless of size/location.
6. Subjects with laboratory or ECG abnormalities (e.g., advanced heart block [second-degree or above atrioventricular block without pacemaker], diagnosis of sick sinus syndrome) considered clinically significant by the investigator or qualified designee and that would have clinical implications for the subject's participation in the study must be excluded.
7. Subjects with serious, unstable, or uncontrolled medical illnesses must be excluded. These include current moderate to severe hepatic impairment, or renal, gastro-enterologic, respiratory, cardiovascular (including ischemic heart disease, congestive heart failure), endocrinologic, or hematologic disease.
8. Subjects who have received an investigational drug within 30 days prior to Screening must be excluded.
9. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine or who are unable to use the sublingual film must be excluded, e.g., subjects with a history of allergic reactions to dexmedetomidine.
10. Subjects whose agitation is attributed to pain or infection, concomitant medication, environmental conditions, or psychiatric condition other than dementia as determined by the investigator.
11. Subjects with any other condition, which in the judgment of the investigator would prevent them from entering or completing the study, such as recent clinical weight loss, chronic dehydration, or a recent clinically significant infection are excluded.

12. Subjects who are currently suffering from substance abuse.
13. Subjects who have had surgery within 30 days prior to Screening or scheduled surgery during the study period.
14. Subjects who are pregnant or breast feeding.
15. Patients with a potential cause for delirium (relatively recent onset agitation and dementia).

9.1.3. Randomization criteria prior to dosing the first dose of study drug

1. Subjects must have a total score ≥14 on the PEC scale
2. Subjects who are judged to be clinically agitated at pre-dose with a total score of ≥8 on the 4 items (aberrant vocalization, motor agitation, aggressiveness, and resisting care) comprising the Pittsburgh Agitation Scale (PAS).

9.1.4. Criterion for dosing study drug for subsequent episodes of agitation

Subjects must have a total score ≥14 on the PEC scale.

9.2. Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from participation in this study at any time for any reason and without prejudice.

The investigator may terminate dosing for a subject at any time for lack of therapeutic effect, intolerability to the subject or reportable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or unsuitability for the study in the investigator's opinion to protect the subject's best interest.

If a subject is withdrawn from dosing before completing the study, the reason for withdrawal will be entered on the appropriate case report form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation of dosing. Subjects who discontinue from the study will not be replaced.

10. STUDY TREATMENTS

10.1. Method of Assigning Subjects to Treatment Groups

Upon confirmation of eligibility following Screening and Pre-dose assessments, subjects will be randomized 1:1:1 to receive BXCL501 40 µg, BXCL501 60 µg, or matching placebo film. Randomization will be stratified based on antipsychotic use in the past month.

Study randomization will be computer generated.

10.2. Identification of Investigational Product

BXCL501 will be provided as a thin, solid-dose film formulation of dexmedetomidine, approximately 286 mm^2 in area, designed to dissolve in the sublingual. Dosing delivers 40 µg or 60 µg sublingually.

Matching placebo films will be provided.

10.3. Treatment Administration

At the time of dosing, subjects will be instructed on how to take the investigational product sublingually and be made aware that they should retain the investigational product in the sublingual until dissolved. The subject will self-administer under the supervision of trained research staff. Placement of the strip will be confirmed and documented. The oral cavity will be checked for irritation periodically after dosing and over the course of the study. Participants will be allowed fluids as desired at least 15 minutes after completion of dosing. If the subject is unable to self-administer and has not received drug, the event will be recorded, and the subject's participation will continue in order to ascertain the number of agitation episodes for which the subject was able to self-administer and the number of agitation episodes for which the subject was not able to self-administer.

10.4. Storage

BXCL501 packaged films must be stored at room temperature (20-25°C/68-77°F with allowed excursion of 15-30°C/59-86°F). Store in the original package.

10.5. Labeling

Each container of study drug will be labeled with study-specific information that meets all applicable regulatory requirements.

10.6. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received study drug. The investigator will not supply study drug to any person except those named as sub-investigators on the FDA 1572, designated staff, and subjects in this study. The investigator will not dispense study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of study drug will be reconciled by the investigator and returned to the sponsor or destroyed as directed.

10.7. Blinding and Unblinding Treatment Assignment

The subject, investigator and study staff will be blinded to study treatment. BXCL501 or placebo film will be provided and administered per Section 10.3 of this protocol.

Treatment assignment for an individual subject should be unblinded only in an emergency, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The investigator should contact the medical monitor before unblinding, when possible, but priority should be given to treatment of the subject. If unblinding occurs without prior approval, the investigator should promptly communicate the circumstances leading to the unblinding by telephone and in writing to the medical monitor.

Breaking of the blind, other than as described above, will be considered a protocol violation. For any subject whose study drug treatment is unblinded, the date, time, and reason for the unblinding must be documented.

10.8. Selection of Dose in the Study

Previous clinical studies with the sublingual film, described above in Section 6.4, provide direct evidence that the exposures from the film are substantially lower than those achieved with the approved intravenous formulation. In translational proof of confidence studies using IV dexmedetomidine in healthy elderly volunteers, agitated patients with schizophrenia as well as agitated elderly patients with dementia, IV infusion achieved calming effects with exposures in the range of proposed doses for this trial (10 µg to 180 µg BXCL501). In agitated patients, mild calming effects became evident with plasma exposures that equate with a 20 µg to 40 µg BXCL501 dose. Across translational studies using IV administration and studies delivering dexmedetomidine via BXCL501, relative to approved IV dexmedetomidine use, low exposure was safe and well-tolerated demonstrating calming effects without excessive sedation in agitated populations. There were also no serious or severe adverse events, or clinically meaningful changes in heart rate or blood pressure.

Study BXCL501-103 assessed efficacy, PK, safety, and tolerability of BXCL501 doses of 30 µg, 60 µg, and 90 µg in adult (65 years and older) males and females with acute agitation associated with dementia. The primary efficacy endpoint was met in both the BXCL501 30 µg and 60 µg treatment groups. At 2 hours post-dose, significant improvements (ie, decreases) from baseline in PEC total scores were observed in the BXCL501 60 µg and BXCL501 30 µg treatment groups compared to placebo. Mean changes from baseline were -7.1 points and -5.7, respectively, versus -2.5 for placebo. LSM differences from placebo were -4.6 (P = 0.0002) and -3.2 (P = 0.0149) for the BXCL501 60 µg and 30 µg treatment groups, respectively (see Section 6.4.4).

The most frequently reported TEAE in the BXCL501 30 µg, 60 µg, and 90 µg treatment groups was somnolence (56.3% [n=9], 60.0% [n=12], and 75.0% [n=3], respectively); placebo was 0%. All cases of somnolence were considered by the investigator to be mild in severity, with the exception of 1 subject (103-01-037) in the BXCL501 60 µg whose case was considered to be moderate in severity and not serious.

Hypotension was reported in only 3 subjects, of which 2 subjects were in the BXCL501 60 µg group (severity was mild in 1 subject and moderate in the other subject) and 1 subject was in the BXCL501 90 µg group (severity was mild). No syncope or falls were reported.

In Study BXCL501-301 (schizophrenic population) and Study BXCL501-302 (bipolar disorder population) single doses up to 180 ug were administered with no serious adverse effects (see Section 6.4.1 and Section 6.4.2, respectively).

10.9. Treatment Compliance

Drug accountability will be performed by site personnel and the drug administration compliance is expected to be 100%.

10.10. Concomitant Medications

All concomitant medications used (including over-the-counter medications and herbal and nutritional supplements) will be recorded in the source document and on the appropriate CRF. The medication name, dose, frequency, date, and indication for use must be recorded on the CRF. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the investigational product may be given at the discretion of the investigator.

10.10.1. Permitted Therapies

Concomitant medications, such as those used for the treatment of agitation, are allowed, with some potential restrictions (see Table 10.1). Other concomitant medications are allowed unless specifically prohibited (see Table 10.1), but should be limited to only those medications considered necessary. Smoking is allowed according to the site policies.

Rescue Medication

At the discretion of the investigator, rescue therapy may be initiated using standard of care treatment for acute agitation. The use of lorazepam is discouraged. When rescue administration occurs, the medication, time, dose, and indication must be clearly recorded as 'For agitation' in the CRF and source documents.

Medications for Insomnia

Benzodiazepines may be administered for insomnia. Administration may not occur sooner than 4 hours after dosing of study treatment and the indication (insomnia) must be clearly recorded in the CRF and source documents.

10.10.2. Prohibited Therapies

A list of prohibited medications prior to and after dosing is provided in Table 10.1.

Patients may receive concomitant medications listed in Table 10.1 on a routine daily, or as needed basis. Therefore, to ensure patient safety and allow any sedative or calming effect of the listed prohibited medication to become apparent, investigators should make every attempt to allow 4 hours to elapse after a prohibited medication to assess the agitation, it's improvement, continuation or worsening.

If the subject's agitation is not improving, continuing or worsening, after 2 hours of receiving a prohibited medication, investigators may proceed with the Pre-dose assessments. For these subjects, 4 hours may not have elapsed and this would not be a protocol violation.

Table 10.1: List of Prohibited Medications Prior to and After Investigational Product Dosing

If possible, within 4 hours prior to dosing of the investigational product the following medications should not be administered
Sedative/hypnotics Barbiturates Anxiolytics (including benzodiazepines) Antihistamines (e.g., diphenhydramine) Sedating antidepressants (mirtazapine, trazodone) Triptans (e.g., sumatriptan) or other serotonin-agonist medications for migraine Opioids
The following medications are prohibited from the time the episode of agitation is identified until 4 hours post-dose, unless clinically indicated
Antiarrhythmics Antibiotics/antifungals/antivirals Anticholinergics Anticonvulsants Antihypertensives (specifically other alpha-adrenergic medications including clonidine, guanfacine, and prazosin) Anxiolytics or sedative-hypnotics Centrally acting calcium antagonist Cholinomimetics Triptans or other migraine-serotonin receptor agonists Opioids
At the discretion of the investigator antihypertensives or other medications may be held on the day of dosing to ensure and maintain subject safety before and after investigational product dosing. *When possible, antipsychotics should not be administered within 4 hours prior to dosing of the investigational product.*

11. STUDY PROCEDURES

Subjects or their LAR will provide written informed consent (in person or remotely) before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

11.1. Screening (Within 45 days Before the First Dose of Investigational Product)

The Screening Visit may be conducted over more than one day; however, all procedures must be completed prior to subject randomization and within 45 days of signing informed consent.

Screen Failures: Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study at discretion of the investigator. Subjects may only be rescreened one time.

The following procedures will be performed at Screening (refer to the Schedule of Events in Table 3.1):

- Obtain written informed consent from subject or LAR, if applicable. Symptoms, understanding of study, and appropriateness must be documented in source. No study procedures may be performed prior to completion of the ICF process.
- Review inclusion and exclusion criteria
- Collect demographic information
- Record resting and orthostatic vital signs
- Record medical history, including prior therapies (e.g., prescription and non-prescription medications, if known onset and type of dementia)
- Record concomitant medication use
- Physical examination (including weight and height)
- 12-lead ECG with rhythm strip
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Urine pregnancy test
- UDS (note: UDS will be re-collected if more than 21 days have passed since the initial collection at the screening visit)
- UTI
- Johns Hopkins Fall Risk Assessment
- ADAS-Cog 12
- MMSE
- PEC
- PAS
- C-SSRS
- CGI-S

Screening assessments to be performed within 45 days before the first dose of investigational product; the assessments may be conducted over more than one day during the Screening period.

If a subject does not become agitated within the 45-day window, the subject is considered a screen failure. However, that subject can be rescreened one additional time at the discretion of the investigator.

11.2. Pre-Dose (within 90 Minutes Before the Dose of Investigational Product)

The following procedures will be performed at Pre-dose (see Table 3.1):

- Review inclusion and exclusion criteria (before the first dose of study drug only, not at subsequent doses)
- Record resting and orthostatic vital signs
- Record concomitant medication use
- 12-lead ECG with rhythm strip
- Pulse oximetry
- MMSE (before the first dose of study drug only, not at subsequent doses)
- PEC
- PAS
- ACES
- CGI-S
- Record agitation behaviors
- Sublingual (SL) assessment
- PK sampling

Randomization criteria prior to dosing the first dose of study drug are:

1. Subjects must have a total score ≥14 points on the PEC scale
2. Subjects who are judged to be clinically agitated at pre-dose with a total score of ≥8 on the 4 items (aberrant vocalization, motor agitation, aggressiveness, and resisting care) comprising the Pittsburgh Agitation Scale (PAS).

Criterion for dosing study drug for subsequent episodes of agitation:

Subjects must have a total score ≥14 points on the PEC scale.

11.3. Post-Dose Assessments (through post dose day 3)

The following are the post-dose assessments; the specific timepoints are provided in Table 3.1.

- ECG with rhythm strip
- Pulse oximetry
- Resting vital signs
- Orthostatic vital signs
- Physical examination (including weight)
- MMSE

- PEC
- PAS
- ACES
- CGI-S
- CGI-I
- C-SSRS
- Record agitation behaviors
- ADAS-Cog 12 (collected on day 3 only if day 83 or day 84 is the last dose day)
- Sublingual (SL) assessment
- PK sampling
- Safety laboratory assessments
- Drug Likability Scales
- Likability Questionnaire
- Record concomitant medications
- Record adverse events

When the Day2/24 hr and predose visits will occur on the same day, the Day 2/24 hrs assessments (see Appendix 1) will serve as the predose assessments as long as the subject is dosed within 90 minutes of the collection of the Day2/24 hrs assessments. Every effort should be made to collect the PEC, PAS, ACES, and CGI-S within 15 minutes prior to dosing. All post-dose efficacy assessments should be conducted prior to any other assessments at each time point. If subsequent dosing cannot occur within 90 minutes of the collection of the Day2/24 hr assessments, all predose assessments must be recollected as per protocol.

The exception are those assessments (see Appendix 1), as these must be completed as part of the predose assessments before every dose.

Assessments done at Day 2/24 hrs that are also being used as predose assessments should be captured as the Day 2/24 hrs assessment data and as the predose data.

11.4. Weekly Assessments (During the 12 Week [day 84/ET] Treatment Period)

Routine assessments will be performed on a weekly basis during the course of the 12 Week (84 days) study and are noted below (see Table 3.2 for specific details). If a dose is administered on the same day or within the window of a scheduled weekly assessment, all dosing assessments will be performed in lieu of the scheduled weekly assessment. If a 24 hour post-dose assessment coincides with a weekly assessment, then the post-dose 24 hour assessment will take precedence. Safety laboratory assessments should be conducted if they are scheduled as part of the weekly visit even though they are not part of the 24 hour post-dose assessments.

- ECG with rhythm strip
- Resting vital signs
- Orthostatic vital signs

- C-SSRS
- MMSE
- Physical exam (including body weight)
- Safety laboratory assessments
- Sublingual (SL) assessment
- Record concomitant medications
- Record adverse events

11.5. Premature Discontinuation (Withdrawal)

As provided in Section 9.2, a subject can voluntarily withdraw from participation in the study or can be withdrawn from the study at the discretion of the investigator.

Whenever possible and reasonable, evaluations that were scheduled for study completion (as listed above in Table 3.2 should be performed at the time of premature discontinuation of dosing.

The Investigator should make every effort should be made to encourage the subject to follow all procedures outlined in the protocol including self-administration of the film. After 3 attempts if the subject still refuses, that subject will be discontinued from the study.

12. STUDY ASSESSMENTS

12.1. Efficacy

The effect of study drug will be evaluated using several validated instruments as described below. All rating assessments will be performed by trained research staff.

12.1.1. PANSS-Excited Component (PEC)

Assessment of drug effect on acute agitation will be done using the Positive and Negative Syndrome Scale – Excited Component (PEC). The PEC comprises 5 items associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each scored 1 (minimum) to 7 (maximum). The PEC, the sum of these 5 subscales, thus ranges from 5 (absence of agitation) to 35 (extremely severe) (Montoya, Valladares et al. 2011).

12.1.2. Pittsburgh Agitation Scale (PAS)

The Pittsburgh Agitation Scale (PAS) is an instrument based on direct observations of the patient that is developed to monitor the severity of agitation associated with dementia. There are 4 behavior groups observed (using a 0 to 4-point scale) in the patient, Aberrant Vocalization, Motor Agitation, Aggressiveness, Resting Care (Rosen et al, 1994).

12.1.3. Agitation-Calmness Evaluation Scale (ACES)

The ACES is a single item measure rating overall agitation and sedation, 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 (Ono, 2007).

12.1.4. CGI-S and CGI-I

Both CGI-I and CGI-S will be focused on the severity of agitation rather than the severity of the overall illness of dementia.

12.1.4.1. CGI-S

Clinical Global Impression of Severity (CGI-S) will be rated based upon the severity of agitation at Screening and Pre-dose (immediately prior to start of dosing).

Severity of agitation will be assessed based on following scale:

0 = Not assessed
1 = Normal not at all symptomatic
2 = Mildly symptomatic-low level of symptoms-little interference in social functioning
3 = Moderately symptomatic-some prominent symptoms-some interference in functioning
4 = Severely symptomatic- very marked symptoms make it difficult for patients to engage with others

12.1.4.2. CGI-I

Drug response on agitation will be evaluated by the Clinical Global Impressions – Improvement (CGI-I) which is performed after dosing. Please rate the current level of agitation relative his/her

level of agitation before administration of the study drug using the following rating scores. A score of "0" indicates an assessment was not conducted.

The CGI-I scores range from 1 to 7:

1=very much improved,
2=much improved,
3=minimally improved,
4=no change,
5=minimally worse,
6=much worse,
7=very much worse

12.1.5. Drug Likability Scale

After dosing with the study drug, subjects will assess their preference of the study drug by answering the statements "I like the taste of the medication" and "The medication is acceptable" using a 5-level Likert scale shown below:

- Strongly disagree
- Disagree
- Neither agree nor disagree
- Agree
- Strongly agree

12.1.6. Drug Likability Questionnaire

Subjects will respond to open-ended questions regarding their experience. Additional comments about aftertaste, smell, dissolve time, etc. will be asked as Yes/No questions with Yes responses prompting an explanation field.

12.2. Clinical Diagnosis and Description of Dementia

The subtype of dementia will be determined and recorded based upon clinical neurologic and psychiatric evaluation to include review of all available medical information, medical records, documentation of prior evaluations, family/caretaker interviews, records, laboratory, genetics or other biomarkers, and results of neuroimaging (if available).

The following will characterize subject's dementia (DSM-5 Major Neurocognitive disorder) in terms of cognitive and functional impairment.

12.2.1. International Psychogeriatric Association Criteria for Agitation

Inclusion criterion #4 for this study is: subjects are expected to exhibit behaviors that are congruent with the International Psychogeriatric Association (IPA) criteria for agitation representing a change from the subject's usual behavior. The process and the criteria for agitation developed by the IPA are explained below.

The IPA formed an Agitation Definition Work Group (ADWG) to develop a provisional consensus definition of agitation in patients with cognitive disorders that can be applied in epidemiologic, non-interventional clinical, pharmacologic, non-pharmacologic interventional,

and neurobiological studies. A consensus definition will facilitate communication and cross-study comparison and may have regulatory applications in drug development programs. The ADWG conducted a broadly inclusive process, involving the IPA and its affiliate members, employing electronic means of participant engagement, holding a face-to-face meeting with international representation, and using survey-based methods. The ADWG was made up of the IPA leadership and other stakeholders interested in the neuropsychiatric aspects of AD and other disorders. The ADWG implemented a transparent process that included nearly 1,000 survey respondents and engaged the memberships of the IPA, IPA affiliates, and other organizations involved in the care and research of neuropsychiatric disorders in patients with cognitive impairment.

A consensus definition of agitation was developed and the criteria are as follows:

Agitation was defined broadly as: (1) occurring in patients with a cognitive impairment or dementia syndrome; (2) exhibiting behavior consistent with emotional distress; (3) manifesting excessive motor activity, verbal aggression, or physical aggression; and (4) evidencing behaviors that cause excess disability and are not solely attributable to another disorder (psychiatric, medical, or substance-related). A majority of the respondents rated all surveyed elements of the definition as “strongly agree” or “somewhat agree” (68–88% across elements). A majority of the respondents agreed that the definition is appropriate for clinical and research applications (Cummings et al, 2015).

12.2.2. MMSE

The Folstein Mini-Mental State Exam (MMSE) is an exam that tests an elderly person's cognitive ability. Domains measured by the MMSE include orientation to time and place, registration, attention and calculation, recall, naming, repetition, comprehension, reading, writing, and drawing. The maximum total points on this test is 30. Table 12.1 provides an interpretation of MMSE scores.

Patients in this study will have score of 15 to 23 on the MMSE at Screening and at Pre-dose (see inclusion criterion #5)

Table 12.1: Interpretation of Mini-Mental State Examination Scores

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with activities of daily living.

Source: Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975 Nov;12(3):189-98.

12.2.3. Alzheimer's Disease Assessment Scale-Cognitive Subscale 12

The Alzheimer's Disease Assessment Scale - Cognitive Subscale 12 (ADAS-Cog) was developed in the 1980s to assess the level of cognitive dysfunction in AD. Although the ADAS-Cog was designed for people with AD, the ADAS-Cog has also been used as an outcome measure for studies of interventions in people with MCI. It is also used for assessing the efficacy of antidementia treatments (Kueper et al., 2018; Skinner et al., 2012). The cognitive subscale of the original ADAS-Cog includes tasks that include both subject-completed tests and rater-based assessments. Together these tasks assess the cognitive domains of memory, language, orientation and praxis.

The ADAS-Cog12 includes the following: Word Recall, Naming Objects and Fingers, Following Commands, Delayed Word Recall, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition, Remembering Test Directions, Spoken Language, Comprehension, and Word Finding Difficulty (Kueper et al., 2018; Schafer et al., 2015).

12.3. Pharmacokinetics

Blood samples (4 mL) for PK analysis will be collected at pre-dose, and at 1, 2, 4, and 8 hours after the first dose and fifth dose of study drug only. However, if the investigator documents it is not appropriate to collect a sample from the subject (e.g., inability to access a venous site to collect a blood sample due to psychomotor agitation, subject refusal, subject's current physical condition) at any of the scheduled timepoints, this will not result in the ineligibility of the subject's participation, should not result in early termination nor will be considered a protocol deviation. All PK collections will have a window of ± 10 minutes post-dose. All PK sampling will occur only after all other assessments at that timepoint are conducted (see Table 3.1).

The plasma concentration-time data will be analyzed by population PK methods. The sparse PK data obtained in this study will be added to the popPK model that has been developed for the drug, to update the model and determine exposure measures for this study. Additional analysis,

such as exposure-response analysis may be conducted based on available data. The methods for and results of these analyses will be reportedly separately, and a summary may be included in the CSR for this study.

12.3.1. Sample Collection & Processing

Details of the sample process will be provided in a PK sample manual, but it is envisioned to be the following process:

- Blood samples will be collected in 4 mL vacutainer tubes containing dipotassium ethylenediaminetetraacetic acid (K2EDTA).
- The time and date of the collection of each blood sample will be recorded.
- After the blood sample has been drawn into the vacutainer tube, it will be gently inverted at least 8 times, permitting the blood specimen to mix with the anticoagulant and avoid clotting of the sample.
- Keep the tubes on ice until the blood samples can be centrifuged. Within 15 minutes of collection, centrifuge blood samples at approximately 1500 g for 15 minutes at approximately 4°C.
- Labels will contain the following information: study number, subject number, study day, time point of sample collection (e.g., 2 hours post-dose), and aliquot/matrix (e.g., plasma primary aliquot or plasma secondary aliquot). Harvested plasma samples will be quick frozen over dry ice immediately.

12.3.2. Sample Storage

Plasma samples will be placed in a storage freezer at -70°C to -80°C or on dry ice within 60 minutes of the blood collection. Samples should be placed in a -70°C to -80°C freezer until they are shipped to the bioanalytical laboratory. Freezers set at -20°C can also be used for a short period of time (maximum 1 month) until they must be shipped to the bioanalytical laboratory.

12.3.3. Sample Shipment

Prior to shipment, the samples will be appropriately packed into a Styrofoam cooler containing dry ice.

- Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 72 hours for remote shipments.
- Samples will be shipped in two aliquots. The second set will be shipped once the status of the first set has been verified.
- The site staff will maintain an inventory of the samples that are to be shipped to the bioanalytical laboratory, including the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. A copy of the inventory will accompany the frozen PK samples.
- The samples will be tracked to ensure arrival in a safe and timely manner.

- Samples will be shipped to:

Northeast Bioanalytical Laboratories LLC
925 Sherman Ave
Hamden, CT 06514
Tel: 203-361-3768
Cell: 203-606-8840

12.4. Analytical Procedures

12.4.1. Bioanalytical Sample Analyses

A validated liquid chromatography-tandem mass spectrometry procedure will be used to measure plasma concentrations of dexmedetomidine (BXCL501) and relevant metabolites. Samples from subjects who have at least 1 post-dose sample will be analyzed.

The bioanalytical report of the assay of the samples will be included in the final report. Analytical results will be presented in tabular form in the final report and chromatographic and derived data will also be provided. Additionally, accuracy, precision, and linearity data for each standard curve and all quality control samples may be presented. Representative chromatograms and standard curve graphs may be included. A bioanalytical sample analysis report with quality assurance statement will be included in the final clinical study report (CSR). Copies of serially selected sample chromatograms for 20% of all samples may be included in the final report.

12.5. Safety

During the study, AEs, clinical laboratory tests, 12-lead ECG with rhythm strip, pulse oximetry, and vital signs will be monitored for tolerability assessment. All observed and volunteered AEs will be recorded. The relationship of AEs to the study drug will be graded as not related, unlikely/remotely related, possibly related, probably related or definitely related by the investigators. Vital signs including SBP, DBP, HR, along with orthostatic vital signs will be monitored. Any abnormal clinically significant (investigator determined) vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter will be repeated until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be of no clinical significance.

12.5.1. Adverse Events

12.5.1.1. Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the product, whether or not it is related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the investigator brochure. For a marketed drug, the known information is in the current package insert.

An unexpected AE is one for which the specificity or severity is not consistent with the current investigator brochure or package insert. For example, hepatic necrosis would be unexpected (greater severity) if the investigator brochure or package insert only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the investigator brochure or package insert only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the medical monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

12.5.1.2. Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the CRF and reported to the medical monitor. Serious adverse events and AEs will be collected after the administration of the first dose of investigational product, after all subsequent dose administrations as well as throughout the study.

At each visit, subjects will be asked for any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented based on all available source data (e.g., clinical laboratory values, physical examination findings, ECG changes, etc) or other documents that are relevant to subject safety.

12.5.1.3. Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dose, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. A recent version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator or designee must report any AE that meets the criteria for an SAE (Section 12.5.1.1) to BioXcel's vendor designee within 24 hours of first becoming aware of the event by e-mail or fax using an SAE report form. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Investigator information (name, phone, fax, e-mail)
- Protocol number
- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, any actions taken, and, if available, the relationship of the AE to the study drug and study conduct.

. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. The investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of the institutional review board (IRB).

SAEs will be reported to BioXcel's vendor designee (s) as per the current Safety Monitoring Plan associated with this study.

12.5.1.3.1. Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

Mild:	Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe:	Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. Serious AEs characterized as intermittent require documentation of onset and duration of each episode.

12.5.1.3.2. Assessment of Relationship

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Not related:	An AE with enough evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, another cause was proven.)
Unlikely/Remotely related:	An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related:	An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related:	An AE with a reasonable time temporal sequence from administration of the study drug; or the AE follows a known pattern of or response to the study drug; or an alternative explanation (e.g., concomitant disease, environment factors, and/or concomitant medications) is less likely than attribution to the study drug; or the AE diminishes or disappears upon cessation of study drug.
Definitely Related:	An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

12.5.1.3.3. Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as "resolved", "resolved with sequelae", "ongoing", "death", "other", or "unknown".

"Death" should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

12.5.1.4. Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after dosing with study drug) to a satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the subject to be stable. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF.

12.5.2. Johns Hopkins Fall Risk Assessment Tool

The Johns Hopkins Fall Risk Assessment Tool (Acute Care Tool) is a validated risk stratification tool to facilitate early detection of risk of falling in adult inpatients by assessing various point-based criteria to derive a total risk score.

The assessment will be conducted at the Screening visit (see Table 3.1).

12.5.3. C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo, 2003) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS assessment will be conducted at Screening (see Table 3.1 and at other timepoints listed in Table 3.2).

12.5.4. Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events tables (Table 3.1 and Table 3.2). Laboratory assessments will be performed by a central laboratory. NOTE: In cases where repeat laboratory tests may be required to confirm eligibility prior to dosing, a local laboratory may be used to obtain repeat test results.

Hematology:	Screening and weekly timepoints Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serum chemistry:	Screening and weekly timepoints Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose, albumin, total protein, and electrolytes (sodium, chloride, potassium, and bicarbonate)
Urinalysis:	Screening and weekly timepoints

	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test:	Screening Women of child-bearing potential only
Urine drug screen:	Screening Cocaine, amphetamine, phencyclidine, benzodiazepines, marijuana. (Note; marijuana positive is allowed provided subject is not moderately to severely dependent, benzodiazepine positive are allowed if prescribed)

12.5.5. Vital Signs

Resting vital signs, including systolic, diastolic blood pressure and heart rate (measured as pulse) will be measured after the subject has been in a **recumbent position for at least 5 minutes** at the time points specified in the schedule of events. Measurements should be made at least 1 minute apart using the same arm at each visit.

Orthostatic measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) will be done with subjects standing and measurements taken after 1, 3, and 5 minutes, per Centers for Disease Control and Prevention guidelines for elderly at Screening, at Pre-dose, and at 1, 2, 4, 8, and 24 (Day 2) hours post-dose, and on Day 3 post-dose.

A change from supine to standing of 20 mmHg SBP or 10 mmHg DBP must be repeated. If any one of the three orthostatic BP readings (1, 3 and/or 5 mins) show a decrease, from supine to standing, of 20 mmHg SBP or 10 mmHg DBP, the entire process needs to be repeated, which includes repeating the resting and orthostatic BPs.

In non-ambulatory subjects, those who are unable to stand, orthostatic vital sign measurements will not be taken. This will not constitute a protocol deviation.

Temperature and respiratory rate will be recorded when orthostatic measurement is indicated in the schedule of events and are not required to be measured at resting vital sign timepoints.

12.5.6. Electrocardiogram

A 12-lead ECG with rhythm strip will be performed at Screening, Pre-dose, Post-dose, and at specific timepoints during the 12 week treatment period. Details are provided in Table 3.1 and Table 3.2.

Each site will be provided with an ECG machine. The ECG data (triplicate ECGs are to be obtained, approximately 1-3 minutes apart from each site will be sent to a central specialist for further assessment. The Principal Investigator must review the ECG to ensure eligibility and safety of the subject.

12.5.7. Physical Examination

A standard physical examination will be performed and will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Physical examinations will be performed at Screening Table 3.1 and at other timepoints listed in Table 3.2.

12.5.8. Concomitant Medications

Concomitant medications will be reviewed and documented throughout the entire 12 week study period. Please refer to Section 10.10 for more details regarding permitted and prohibited concomitant medications.

13. STATISTICAL METHODS

13.1. General Considerations

A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be finalized before database lock.

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by treatment group for evaluated variables.

All statistical tests and confidence intervals, unless stated otherwise, are 2-sided and will be set at α=0.05.

13.2. Analysis Populations

The following analysis populations are planned:

- Safety Population: All subjects receiving at least 1 dose of study drug, with subjects classified according to the drug actually received.
- Full Analysis Set: All subjects who take any study medication and who had both baseline and at least one efficacy assessment after dosing.

13.3. Statistical Analyses

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. Baseline is defined as the last observation prior to initiation of study drug. Missing data is not anticipated at the 2 hour primary time point. Details of the statistical analyses will be provided in the SAP, which will be finalized prior to database lock.

13.3.1. Subject Disposition and Demographic Characteristics

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment.

Demographics and baseline characteristics, including age, sex, race, weight, height, and body mass index, will be summarized by treatment for the Safety Population.

13.3.2. Efficacy Analyses

Efficacy analyses will use data from the full analysis set (FAS) as the target population, defined as all subjects who take any study medication and who had both baseline and at least one efficacy assessment after dosing. Change from baseline (pre-dose) in the PEC at 2 hours post-dose for the first treated agitation episode will be considered primary.

Efficacy analyses for measures assessed at specific scheduled time points will evaluate the change from baseline using a mixed model repeated measures (MMRM).

Additional details regarding analysis models, control for multiplicity and sensitivity analyses in the event of missing data associated with intercurrent events of specific types will be included in the statistical analysis plan.

13.3.2.1. Primary Efficacy Analysis

The change from baseline in PEC total score at 2 hours post-dose for the first treated episode of agitation constitutes the primary endpoint for this study. Table 13.1 provides the information for the four estimand attributes needed for the primary efficacy analysis.

Table 13.1: Estimand Attributes for the Primary Efficacy Analysis

Estimand attribute	Description of attribute
Target population	FAS population - All patients who take any study medication and who had both baseline and at least one dose of study drug.
Primary endpoint	Absolute change from baseline in the total PEC score at 2 hours post-dose for the first treated episode of agitation.
Handling of intercurrent events	All values collected after the use of rescue treatment and withdrawal from study will be used in the analysis (treatment policy strategy).
Population-level summary	Difference between dose-specific treatment arm and placebo arm in mean change from baseline in the total PEC at 2 hours using all measurements from baseline through 4 hours.

Abbreviations: FAS = Full Analysis Set; PEC = Positive and Negative Syndrome Scale – Excited Component

The null and alternative hypotheses to be tested for the primary endpoint are stated as H01: $\Delta_{BXCL501\_60} = \Delta_{PBO}$ and HA1: $\Delta_{BXCL501\_60} \neq \Delta_{PBO}$ and H02: $\Delta_{BXCL501\_40} = \Delta_{PBO}$ and HA2: $\Delta_{BXCL501\_40} \neq \Delta_{PBO}$, where $\Delta_{BXCL501\_60}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 60 µg group, $\Delta_{BXCL501\_40}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 40 µg group, and Δ_{PBO} denotes the change from baseline in the PEC at 2 hours post-dose in the placebo group. These hypotheses will be tested using a mixed model repeated measures (MMRM) model. To account for the testing of two hypotheses, the two-sided significance level for each test will be determined using the Bonferroni correction with each hypothesis tested at a significance level of 0.025.

The MMRM will include the change from baseline in the PEC at 30 minutes, 1 hour, 2 hours, and 4 hours post-dose as the outcome and the baseline PEC, treatment group, antipsychotic use (stratification factor), visit number, and a treatment group by visit number interaction term as covariates.

The model will be fit using an unstructured covariance matrix with the Kenward-Rogers adjustment for the degrees of freedom. As the change from baseline in PEC score is only measured at 30 minutes, 1 hour, 2 hours and 4 hours, the covariance structure includes a total of 10 parameters making the likelihood that the model fails to converge low. In all prior studies of BXCL501 there have been few missing data points in the two-hour assessment window; however, methods to address missing data are proposed as part of the sensitivity analyses.

In the event that the model fails to converge with an unstructured covariance matrix, the following covariance structures will be applied, in order, until convergence is reached: heterogenous Toeplitz structure, Toeplitz structure, auto-regressive of order 1 (AR(1)), and compound symmetry structure. For the alternative covariance structures, the sandwich estimator will be used to obtain the estimates of the standard error and the Kenward-Rogers adjustment for degrees of freedom will not be applicable. If convergence proves to be a problem and an alternative covariance structure is needed there may be an inflation of type I error. To address this, the methods proposed in Lu and Mehrotra (2009) will be used as well with the Fisher scoring algorithm being used to obtain the initial values of the covariance parameters.

The estimated mean difference between the groups treated with either 40 µg or 60 µg BXCL501 and the placebo group in change from baseline in the PEC score will be estimated at 2 hours.

13.3.2.2. Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints are:

- PEC change from baseline at 1 hour post-dose of study treatment for the first episode of agitation (measures *initial* efficacy)
- PEC change from baseline at 30 minutes post-dose of study treatment for the first episode of agitation (measures *initial* efficacy)

The attributes for the estimands of the key secondary endpoints of PEC change from baseline at 1 hour post-dose for the first episode of agitation and the PEC change from baseline at 30 minutes post-dose for the first episode of agitation are provided in Table 13.2.

Table 13.2: Estimand Attributes for the Key Secondary Analyses of Change from Baseline in total PEC score at 1 hour and at 30 minutes

Estimand attribute	Description of attribute
Target population	FAS population - All patients who take any study medication and who had both baseline and at least one dose of study drug.
Primary endpoint	Absolute change from baseline in the total PEC score at 1 hour or at 30 minutes.
Handling of intercurrent events	All values collected after the use of rescue treatment and withdrawal from study will be used in the analysis (treatment policy strategy).
Population-level summary	Difference between dose-specific treatment arm and placebo arm in mean change from baseline in the total PEC score at 1 hour or at 30 minutes using all measurements from baseline through 4 hours.

Abbreviations: FAS = Full Analysis Set; PEC = Positive and Negative Syndrome Scale – Excited Component

The null and alternative hypotheses to be tested for the two key secondary endpoints listed above are similar to those for the primary endpoint, with the timepoint for testing being 1 hour post-dose for the first key secondary endpoint and 30 minutes post-dose for the second key secondary endpoint. These hypotheses will be tested using the MMRM model described for the primary analysis.

The endpoints, in the order to be tested, are as follows:

1. PEC change from baseline to 1 hour for the first treated episode of agitation.
2. PEC change from baseline to 30 minutes for the first treated episode of agitation.

The fixed-sequence method will be used to adjust for multiplicity and applied to each dose separately. If at any point in the testing, the significance level is greater than 0.025 for the comparison of interest, then all testing ceases for that dose level and the remaining p-values are reported as nominal levels.

13.3.2.3. Continued Efficacy Endpoints

The continued efficacy endpoints and a description of the proposed analysis approach are outlined below.

- PEC change from pre-dose at 2 hours post-dose of study treatment for the last treated episode of agitation. This endpoint will be analyzed using the MMRM model that is used for the primary analysis.
- PEC change from pre-dose at 2 hours post-dose of study treatment for all treated episodes of agitation. This is a multivariate endpoint consisting of the PEC change from pre-dose at 2 hours post-dose of study treatment for all treated episodes of agitation. The null hypothesis being tested is that there is no decline in treatment effect over all episodes of agitation. The model has been parametrized with the PEC change from pre-dose at 2 hours post-dose for each treated episode of agitation as the outcome and the following covariates: baseline pre-dose PEC value for the treated episode, number of episodes, time (days) of the treated episode, trt_40 which is an indicator variable that is equal to 1 for all subjects in the BXCL 40 µg group and 0 otherwise, trt_60 which is an indicator variable that is equal to 1 for all subjects in the BXCL 60 µg group and 0 otherwise, and interaction term of time and trt_40, and an interaction term of time and trt_60. Details of the analysis approach will be provided the statistical analysis plan (SAP.)
- Percentage of all treated episodes of agitation satisfying the definition of PEC responder, an episode with at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment will be analyzed using an ANCOVA model with percentage of episodes meeting the definition of PEC responder as the outcome, and treatment group and antipsychotic use (stratification factor) as covariates. A weighted least squares approach may also be used to account for the differing number of episodes across subjects.
- Percentage of all treated episodes of agitation for which the PEC change from pre dose at 2 hours post-dose of study treatment is a reduction of at least 5 points (measures continued efficacy) will be analyzed using an ANCOVA model with percentage of episodes meeting the definition of PEC responder as the outcome, and treatment group and antipsychotic use (stratification factor) as covariates. A weighted least squares approach may also be used to account for the differing number of episodes across subjects.
- Average PEC change from pre-dose at 2 hours post-dose of study treatment over all treated episodes of agitation. This is a single endpoint which is computed based on the

averaging the change from pre-dose at 2 hours post dose of study treatment across all treated episodes. An ANCOVA model will be used for this analysis. The model will include the average change from pre-dose in PEC score at 2 hours over all episodes as the outcome, and treatment group and antipsychotic use (stratification factor) as covariates. A weighted least squares approach may also be used to account for the differing number of episodes across subjects.

- Subgroup of subjects with at least two treated episodes of agitation with an endpoint of the PEC change from pre-dose at 2 hours post-dose of study treatment for the second episode of agitation. For this analysis, the MMRM model described for the primary analysis will be used.
- Subgroup of subjects with at least three episodes of treated agitation with an endpoint of the PEC change from pre-dose at 2 hours post-dose of study treatment for the third episode of agitation. For this analysis, the MMRM model described for the primary analysis will be used.
- Severity of each treated episode of agitation at pre-dose, as measured by PEC (measures continued efficacy) will be analyzed using a longitudinal mixed model with the outcome being the pre-dose PEC value at each episode. Time is defined as the time of the episode in study day (ranging from 1 to 84 days). The model will include an intercept as a random effect, treatment group as a class variable, antipsychotic use (stratification factor), and a time by treatment group interaction term as fixed effects. The model will be fit with no fixed effect intercept term. Under this model the null hypothesis that the slope measuring the rate of change of the pre dose PEC score across all treated episodes is zero will be tested. Details of the analysis approach will be provided the statistical analysis plan (SAP.)
- Frequency of treated episodes of agitation (measures continued efficacy). This is a single outcome defined as the number of treated episodes of agitation for each subject. It will be assessed with a Poisson model that includes treatment group and antipsychotic use (stratification factor) as covariates. The results will be summarized as an incidence rate ratio and the significance level for the test of the null hypothesis of no difference between each dose level and placebo will be obtained from the significance level for the test of each dose level versus placebo.
- PEC change from pre-dose at 2 hours post-dose of study treatment at the last treated episode of agitation –PEC change from pre-dose at 2 hours post-dose of study treatment at the first treated episode of agitation. This is a single outcome. The goal of the proposed analysis is to determine if there is a change in treatment effect when comparing the first and last treated episodes. It is anticipated that there will not be a large difference between the treatment effect at the first and last treated episode for the groups receiving either BXCL501 40 µg or BXCL501 60 µg. The same result is anticipated for the placebo group as well. Thus, it is likely that this will provide a larger significance level with a result of failure to reject the null hypothesis. While this result does not demonstrate that the outcome is the same at the first and last treated episodes, this analysis will contribute to the body of evidence supporting continued efficacy. Details of the analysis approach will be provided the statistical analysis plan (SAP.)

13.3.2.4. Other Secondary Efficacy Endpoints

The methods that will be used to analyze each outcome will be as follows:

- The number of PEC responders (patients who achieve at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment) for the first treated episode of agitation will be analyzed using a stratified Mantel-Haenszel test stratified by antipsychotic use (stratification factor).
- The change from baseline in PAS and CGI-S at 2 hours and the CGI-I at 2 hours post-dose for the first episode of agitation will be analyzed using an ANCOVA model with the change from baseline at 2 hours post-dose as the outcome, and baseline value of the outcome (used only for PAS and CGI-S), antipsychotic use (stratification factor), and treatment group as covariates.
- The number of CGI-I responders (patients who achieve a CGI-I score of 1 or 2 at 2 hours post-dose of study treatment) for the first episode of agitation will be analyzed using a stratified Mantel-Haenszel test, stratifying according to the stratification factor of antipsychotic use.
- The average change in PAS and CGI-S at 2 hours post-dose over all treated episodes of agitation will be analyzed using an ANCOVA model with the average values of change in PAS or CGI-S across all episodes as the outcome, and treatment group and antipsychotic use (stratification factor) as covariates.
- The average CGI-I at 2 hours post-dose over all treated episodes of agitation will be analyzed using an ANCOVA model with the average CGI-I across all episodes as the outcome, treatment group and antipsychotic use (stratification factor) as covariates.
- The percentage of all treated episodes of agitation satisfying the definition of CGI-I responder will be analyzed using an ANCOVA model with treatment group and antipsychotic use (stratification factor) as covariates.
- Average PEC change from pre-dose at 1-hour post-dose of study treatment over all treated episodes of agitation will be analyzed using an ANCOVA model with treatment group and antipsychotic use (stratification factor) as covariates.
- Average PEC change from pre-dose at 30 minutes post-dose of study treatment over all treated episodes of agitation will be analyzed using an ANCOVA model with treatment group and antipsychotic use (stratification factor) as covariates.
- Change from screening in ADAS-Cog 12 at day 84 will be analyzed using a two-sample t-test.
- The change from baseline in ACES scores at 2, 4, and 8 hours post-dose for the first episode of agitation, will be analyzed using an ANCOVA model with the change from baseline in ACES score as the outcome, and the baseline value of the outcome, antipsychotic use (stratification factor), and treatment group as covariates.
- Change from screening in MMSE at Day 28 and at Day 84 will be analyzed using a two-sample t-test.

13.3.3. Safety and Tolerability Analyses

Safety data analysis will be conducted on all subjects receiving at least 1 dose of study drug. The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment, relationship to study drug, and severity. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Listings of subjects who

experience withdrawal due to an AE, SAEs and/or death will be presented. Laboratory parameters will be summarized by treatment using descriptive statistics and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics.

Orthostatic assessments will follow the Centers for Disease Control and Prevention guidelines for the elderly (e.g., BP upon standing for 1, 3, and 5 minutes) (https://www.cdc.gov/steadi/pdf/Measuring_Orthostatic_Blood_Pressure-print.pdf).

Results will be presented for first dose of study drug and for all doses of study drug.

13.4. Sample Size Determination

Approximately 150 subjects are anticipated to be enrolled. Assuming a standard deviation of 4 in change from baseline in the PEC at two hours post-dose and a two-sided two-sample t-test, 150 subjects provides in excess of 90% power to detect a difference in mean PEC score of 2.9 units or more, at the 0.025 alpha-level (adjusted for multiplicity of doses) for either dose versus placebo.

A blinded sample size recalculation is currently planned when approximately 50% of the PEC total score data at 2 hours post initial dose are available. The pooled standard deviation of the change from baseline in PEC total score will be computed at each time point. The sample size will then be recalculated with the potential to adjust the sample size accordingly. Details of the sample size recalculation will be provided in the SAP.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and strict data management procedures.

14.1. Sponsor and Investigator Responsibilities

14.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles. The sponsor reserves the right to withdraw a subject from the study, to terminate participation of a study site at any time, or to discontinue the study.

The sponsor agrees to provide the investigator with enough material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2. Investigator Responsibilities

By signing the Investigator's Agreement, the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Council for Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed consent.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Study Documents

All documentation and material provided by the sponsor for this study are to be retained in a secure location and treated as confidential material.

14.3.1. Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Signature Log/Delegation of Study-related Duties
- FDA Form 1572
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by the sponsor or designee before the study site can initiate the study and before the sponsor will authorize shipment of study drug to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the study drug, CRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

14.3.2. Case Report Forms

By signing the Investigator's Agreement, the investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all subjects who sign an informed consent form.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific CRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the CRF according to the completion guidelines provided by the sponsor or its designee.

The CRFs may be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the CRF is accurate and true.

14.3.3. Source Documents

All information recorded in the CRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

14.4. Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical study.

14.4.1. Monitoring Procedures

The sponsor or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate (CRA) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA and other authorized sponsor personnel access. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA will review:

- Regulatory documents, directly comparing entries in the CRF with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of study drug and study materials

The CRA will ask for clarification or correction of any noted inconsistencies. Procedures for correcting CRFs are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement, the investigator agrees to meet with the CRA during study site visits; to ensure that study staff is available to the CRA as needed; to provide the CRA access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.4.2. Data Management

The sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the sponsor's or contract research organization's (CRO) standard operating procedures. A comprehensive data management plan will be developed including a data management plan,

database contents, annotated CRF, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the Data Management Plan.

14.4.3. Quality Assurance/Audit

This study may be subject to audit by the sponsor or designee. The audits may be undertaken to check compliance with GCP guidelines and may include:

- In-house study file audit
- Audit of computer database quality control
- Audit of clinical report quality control

The sponsor or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

14.5. Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason.

14.5.1. Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, the sponsor or designee will notify the IRB and regulatory authorities about the regular termination of the study as required.

14.5.2. Premature Study Termination

The study may be terminated prematurely for any reason and at any time by the sponsor, IRB, regulatory authorities, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, the sponsor or designee will notify the IRB and regulatory authorities as required. The sponsor or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of subjects to ensure protection of the subjects'

interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination visit.

14.6. Study Site Closure

At the end of the study, all study sites will be closed. The sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol, with applicable regulations and guidelines, or both.
- Inadequate subject enrollment.

14.6.1. Record Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until at least 2 years after the notification of submission of the final CSR to regulatory authorities by the sponsor.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After completing the study, the sponsor will be provided with the original CRFs or at least a legible copy and retain the documents at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files, and other source data until at least 5 years after notification of submission of the final CSR to the regulatory authorities by the sponsor. These documents need to be retained for a longer period if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period permitted by the hospital, institution, or private practice.

14.6.2. Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed or at the completion of the CSR. In addition, identifiable samples can be destroyed at any time at the request of the subject.

14.7. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval by the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency.

14.8. Use of Information

All information about the study drug, the sponsor's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by the sponsor in connection with the continued development of the study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

In order to maintain patient privacy, all CRF, investigational product accountability records, study reports and communications will identify the patient by initials and/or the assigned patient number. The investigator will grant monitor(s) and auditor(s) from BioXcel (or designee) and regulatory authorities access to the patient's original medical records for verification of data gathered on the CRF and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations

15. FINAL CLINICAL STUDY REPORT

The final CSR will be written according to the "Guideline for Industry (Structure and Content of Clinical Study Reports)" from the ICH E3. The final CSR will present a narrative description of the clinical, analytical, PK, and statistical results. Tables and figures will be "integrated" into the main text, with appendices at the end of the report (e.g., the protocol, sample CRFs, investigator-related information, test/reference product information, subject data listings).

The final CSR will be submitted to the appropriate regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP and the 1996 Version of the Declaration of Helsinki.

16.2. Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent has been obtained from the subject or LAR before any activity or procedure is undertaken that is not part of routine care.

16.3. Approval by Institutional Review Board

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the sponsor monitor before shipment of investigational drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by the sponsor before implementation. This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

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18. APPENDIX 1

Appendix Table 1: Day 2 Post-dose Assessments

Activity	Pre-dose -90 min to time 0	Day 2 24 hr
ECG with rhythm strip	*X*	*X*
Pulse oximetry	*X*	*X*
Resting vital signs	*X*	*X*
Orthostatic vital signs	*X*	*X*
Agitation behaviors	**X**	
Study drug administration	**X**	
PAS	*X*	*X*
PEC	*X*	*X*
ACES	*X*	*X*
CGI-Severity (agitation)	**X**	
CGI-Improvement (change in agitation)		X
C-SSRS		
Sublingual (SL) assessment	*X*	*X*
PK sampling	*X*	
Concomitant medications	*X*	*X*
Adverse events		X

Italics denotes the Day 2/24 hrs assessments that will serve as the predose assessments as long as subject is dosed within 90 minutes of the collection of Day2/24 hrs assessments.

Bold denotes the assessments that should be completed as part of the predose assessments before every dose.