STATISTICAL ANALYSIS PLAN
PROTOCOL BXCL501-304

BioXcel Therapeutics, Inc.

Protocol BXCL501-304
A Multicenter, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of PRN Dosing of BXCL501 Over a 12 Week Treatment Period in Subjects with Agitation Associated with Dementia who Require at Least Moderate to Full Assistance with Activities of Daily Living

Statistical Analysis Plan
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ABBREVIATIONS

ACES	Agitation and Calmness Evaluation Scale
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale 12
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BDR	blind data review
BMI	body mass index
BP	blood pressure
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CS	cumulative sum
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
ECG	electrocardiogram
EOS	end of study
FAS	full analysis set
ICF	informed consent form
IUD	intrauterine device
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
NCS	normalized cumulative sum
NIA-AA	National Institute on Aging and Alzheimer's Association
PAS	Pittsburgh Agitation Scale
PEC	Positive and Negative Syndrome Scale – Excited Component
PK	pharmacokinetic
PRN	as needed (pro re nata)
SAP	statistical analysis plan
SBP	systolic blood pressure
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the planned analyses for BioXcel's Protocol BXCL501-304, entitled "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 who require at least moderate to full assistance with their activities of daily living (ADLs)". This SAP is based on Version 2 Amendment 1 of the protocol, dated December 7, 2022.

This SAP is to be interpreted in conjunction with the protocol. Should the SAP and protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. If the final clinical study report (CSR) contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials).

2. Study objectives

2.1. 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 168 doses (with a maximum of 2 doses per day) within a 12-week treatment period.

2.2. Key secondary objective

The key secondary objectives are:

- 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.

3. Study design and conduct

3.1. 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 Alzheimer's disease (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. Prior to screening, subjects will be monitored by the research staff for frequency and characterization of agitation episodes for a period of 2 weeks, if possible, to establish a baseline of frequency.

Subjects will be dosed PRN up to a maximum of two doses per calendar day over the 12-week treatment period. In the event of persistent or recurrent agitation, Investigators may choose to repeat a full dose of study medication (ie, BXCL501 40 μg, BXCL501 60 μg, or matching placebo film) but only after the 2-hour post-dose assessments are completed, and if the PEC change from baseline is ≤40% (but in the absence of safety concerns). If a re-dose will fall outside the 2 hr, 4 hr, 8 hr or 12 hr post first dose assessments, then the PEC assessment should be completed within 15 min before the redose and resting vital signs, orthostatic vital signs and concomitant medications should be collected, if feasible, before the re-dose. If a re-dose is warranted but not administered, then the reason should be documented. Day 84 is the last day a subject may receive a maximum of 2 doses 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. However, every attempt must be made to capture and treat the majority of agitation episodes.

Subjects must reside in a care facility where all study-related procedures and study drug dosing will be performed by trained and delegated staff under the supervision of the Principal Investigator (PI). The PI may have several care facilities under his/her direct supervision with Sub-investigators and trained research staff present at each of these care facilities during dosing and study-related

assessments. If the PI is not physically present on site, they will be available on-call to the sub-investigator and research staff to address any safety concerns that may arise during the conduct of the protocol and procedures.

On each dosing day, and on all follow-up days, the sub-investigator and research staff will monitor the patient and ensure the safety of subjects including following the protocol defined safety procedures. In the event of a safety issue, the PI or Sub-investigator will assess and appropriately treat the patient. If necessary, the sponsor will be informed as well.

In addition, each site has designated research staff who will work in collaboration with the PI and be responsible for assessing the agitation episode to determine eligibility and appropriateness to administer a dose of study drug. The research staff will be present before, during and after dosing to ensure all procedures, rating scales, vital sign monitoring and safety assessments are conducted to monitor the safety of patients during the study. Research staff will also be on call throughout the study.

Every effort should be made to collect blood pressure (BP) and orthostatic (OH) BP 1 hr prior to dosing. For patients who are non-ambulatory, OH BP measurements will be taken from a supine position to a sitting position and analyzed separately from those patients who were able to stand for OH BP measurements. Every effort should be made to ensure all subjects are well-hydrated prior to dosing.

At the time of dosing, subjects will be instructed on how to take the investigational product sublingually or buccally (behind the lower lip between the gum and lip) and be made aware that they should retain the investigational product in the sublingual or buccal space 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. These checks should be performed by the same staff member prior to dosing and at all post dose time points for a subject, when possible. Subjects will not be allowed to eat or drink for at least 15 minutes after sublingual administration, or at least one hour after buccal administration.

Subjects will be encouraged to remain sitting or lying down until effect of the medication is known after dosing.

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 or is unable to self-administer the film that subject will be discontinued.

Safety, efficacy, and tolerability will be measured periodically throughout the treatment period according to the timepoints provided in the Schedule of Events tables (Exhibit 3 and Exhibit 4). 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 2-hour assessments are completed.

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

3.2. Study population

Individuals with a diagnosis of Alzheimer's clinical syndrome based on NIA-AA criteria (Jack et al., 2018) are eligible for enrollment in this study. If subject 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.

Subjects must require moderate to full assistance with their activities of daily living (ADLs) and reside in a facility where such assistance is available. Moderate assistance is defined as the need for physical assistance of another individual for activities such as bathing, eating, dressing, toileting, ambulation, and transfer in and out of bed/chair. Subjects, or their legally authorized representative (LAR), if necessary, will sign an informed consent form (ICF) before any study-related procedures are performed.

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.

Exhibit 1 and Exhibit 2 display the study's inclusion and exclusion criteria, respectively.

Exhibit 1. Inclusion criteria

1. Male and female subjects 65 years and older.
2. All subjects must have a diagnosis of probable Alzheimer's clinical syndromebased on NIA-AA criteria (2018). If subject 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 0 to 20 (moderate to severe) on the Mini-Mental State Exam (MMSE) at Screening and require moderate to full assistance with activities of daily living (defined as the need for physical assistance of another individual for activities such as bathing, eating, dressing, toileting, ambulation, and transfer in and out of bed/chair). Confirmed by Katz index score of 4 or less.
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 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

Exhibit 2. Exclusion criteria

1. Subjects with dementia or other memory impairment not due to probable Alzheimer's clinical syndrome, 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 Alzheimer's disease 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 ideation in the past 6 months and/or suicidal behaviors in the past 2 years, are excluded, or any subject with an answer of "yes" to item 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) for the last 6 months 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.

1. 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 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. Subjects with a potential cause for delirium (relatively recent onset agitation and dementia)

3.3. Study treatment

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.

3.4. Schedule of events

Exhibit 3 and Exhibit 4 display the schedule of events and assessments.

Exhibit 3. 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[12] 24 hr (±2 hrs)
Informed consent	X								
Medical history	X								
Inclusion/Exclusion	X	X[4]							
Demographics	X								
Weight	X								X
Height	X								
Mini-Mental State Exam	X								X
ADAS-Cog 12 Living	X								X
Physical exam	X								
Safety laboratory assessments[5]	X								X
Urine pregnancy test	X								
UDS[6]	X								
Johns Hopkins Fall Risk Assessment	X								
ECG with rhythm strip[7]	X	X			X	X	X	X	X
Pulse oximetry		X			X	X	X	X	X
Resting vital signs[8]	X	X	X	X	X	X	X	X	X
Orthostatic vital signs[9]	X	X		X	X	X	X		X
Randomization		X[4]							
Agitation behaviors		X			X				
Study drug administration[10]		X							
Katz Index	X								
PAS	X	X[2]			X	X	X	X	X
PEC	X	X[2]	X	X	X	X	X	X	X
ACES		X[2]		X	X	X	X	X	X

Exhibit 3. Schedule of events – screening, pre-dose, and post-dose assessments, continued

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[12] 24 hr (±2 hrs)
CGI-Severity (agitation)	X	X[2]			X	X			
CGI-Improvement (change in agitation)			X	X	X	X	X	X	X
C-SSRS	X								X
Sublingual or buccal assessment		X	X		X	X			X
PK sampling[11]		X		X	X	X	X		
Drug Likability Scales						X			
Likability Questionnaire						X			
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X
EQ-5D-5L Caregiver	X								

Abbreviations: ADAS-Cog 12 Living = Alzheimer's Disease Assessment Scale - Cognitive Subscale 12 Living; ACES = Agitation-Calmness Evaluation Scale; 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; EQ-5D-5L = EuroQoL-5 Dimensions-5 Level; 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

Exhibit 3. Schedule of events – screening, pre-dose, and post-dose assessments, continued

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. Subjects may 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, BP and orthostatic BP should be collected within 1 hour prior to dosing. Every effort should be made to collect the PEC, within 15 mins of dosing. The PAS, ACEs, and CGI-S can be conducted within the 90 min window. 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, and will not be considered a protocol deviation.

[4] Review of Inclusion and Exclusion criteria for initial dose only

[5] Safety laboratory assessments will include clinical chemistry, hematology, and urinalysis. In cases where a repeat laboratory test may be required to confirm eligibility prior to dosing, a local laboratory may be used to obtain repeat test results.

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

[7] 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 1-3 minutes apart each time an ECG is required.

[8] 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 30 minutes, 1, 2, 4, 8, 12, and 24 (Day 2) 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.

[9] 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, and 24 (Day 2) hours post-dose. 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, both resting and orthostatic blood pressures must be repeated. For patients who are non-ambulatory, OH BP measurements will be taken from a supine position to a sitting position and analyzed separately from those patients who were able to stand for OH BP measurements. 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.

[10] In the event of persistent or recurrent agitation Investigators may choose to repeat a full dose (re-dose) of study medication (ie, BXCL501 40 µg, BXCL501 60 µg, or matching placebo film) and the PEC change from baseline is ≤40% (but in the absence of safety concerns). A subject may only receive a maximum of 2 doses in a calendar day. If a re-dose is needed in the same calendar day, it cannot be administered until after the 2 hr post dose assessments for the first dose have been completed. Following the administration of the re-dose, all post dose assessments will be completed based on when the re-dose was administered. Assessments at 4 or 8 hours post first dose in a day that occurred within 1 hour of a post re-dose assessment are not required to be performed. If a re-dose will fall outside the 2 hr, 4 hr, 8 hr or 12 hr post first dose assessments, then the PEC assessment should be completed within 15 min before the re-dose and resting vital signs, orthostatic vital signs and concomitant medications should be collected, if feasible, before the re-dose. If a re-dose is warranted but not administered, then the reason should be documented.

[11] 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. Additionally, for subjects who were redosed on the day of the first and fifth dose, a PK blood sample is to be collected at 2 hours after the redose. If the redose was administered at 2 hours or 6 hours post the first dose, then the 4 hour or 8 hour PK blood sample after the first dose will serve as the 2 hour sample after the redose. For any redose that occurs at any other time beyond 3 hours after the first dose, a PK blood sample is to be collected at 2 hours after the redose. 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/dehydration) 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 sampling will occur only after all other assessments at that timepoint are conducted.

[12] If Day 2/24 hr and predose visits will occur on the same day, the Day 2/24 hrs assessments can serve as the predose assessments as long as the subject is dosed within 90 minutes of the collection of the Day 2/24 hrs assessments. 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 Day 2/24 hr assessments, all predose assessments must be recollected. Predose agitation behaviors, and CGI-severity must be completed prior to each dose of study drug.

Exhibit 4. 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
Body weight				X				X				X
Safety laboratory assessments	X		X		X		X		X		X	X
Sublingual or buccal 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
EQ-5D-5L												X

Abbreviations: ADAS-Cog 12 Living = Alzheimer's Disease Assessment Scale - Cognitive Subscale 12 Living; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; EQ-5D-5L = EuroQoL-5 Dimensions-5 Level; 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 perform an ECG due to agitation, it will not constitute a protocol deviation. Triplicate ECGs are to be obtained 1-3 minutes apart each time an ECG is required.

[3] Resting vital signs (SBP, DBP and HR) will be taken upon having the subject recumbent for 5 minutes. Triplicate measurements are 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 decrease from supine to standing of 20 mmHg SBP or 10 mmHg DBP must be repeated.

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. Outcome variable definitions

4.1. Screening and baseline characteristics

Screening characteristics: Inclusion/exclusion criteria, demographic characteristics (age, sex, race, ethnicity), height, weight, medical history, prior and concomitant medications, physical examination, resting and orthostatic vital signs, pregnancy test, urine drug screen, 12-lead electrocardiogram (ECG) in triplicate, clinical laboratory results, Johns Hopkins Fall Risk Assessment, urine drug screen, Mini-Mental State Examination (MMSE), ADAS-Cog 12, Pittsburgh Agitation Scale (PAS), PEC, Clinical Global Impression–Severity (CGI-S), Columbia-Suicide Severity Rating Scale (C-SSRS), Katz Index of Independence in Activities of Daily Living, and EQ-5D-5L Caregiver questionnaire will be collected at Screening.

Baseline characteristics: Eligibility, resting and orthostatic vital signs, concomitant medications, sublingual or buccal assessment, 12-lead electrocardiogram (ECG) in triplicate, CGI-S, PEC, Agitation and Calmness Evaluation Scale (ACES), agitation behaviors (based on list of behaviors provided in the CRF), and pharmacokinetic sampling will be collected prior to dose administration.

4.2. Efficacy assessments

The effect of study drug will be evaluated using several validated instruments as described below.

4.2.1. Positive and Negative Syndrome Scale – Excited Component (PEC)

Assessment of drug effect on acute agitation will be done using the PEC. The PEC comprises 5 items associated with agitation, each scored from 1 (minimum) to 7 (maximum): poor impulse control, tension, hostility, uncooperativeness, and excitement. The PEC is the sum of these 5 subscales and thus ranges from 5 to 35.

4.2.2. Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I)

The CGI-S will be based on the severity of agitation at Screening and pre-dose (immediately prior to start of dosing). The CGI-S scores will assess the severity of illness based on the following scale:

- 0 = not assessed
- 1 = not at all ill
- 2 = borderline mentally ill
- 3 = mildly ill
- 4 = moderately ill
- 5 = markedly ill
- 6 = severely ill
- 7 = among the most extremely ill subjects

Drug response on agitation will be evaluated by the CGI-I. It will be performed at 30 minutes, 1 hour, 2 hours, and 4 hours post-dose. The CGI-I scores range from 1 to 7:

- 0 = not assessed (missing)
- 1 = very much improved
- 2 = much improved
- 3 = minimally improved
- 4 = no change
- 5 = minimally worse
- 6 = much worse
- 7 = very much worse

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

4.2.3. Agitation-Calmness Evaluation Scale (ACES)

The ACES is a single-item measure rating overall agitation and sedation from 1 to 9:

- 1 = marked agitation
- 2 = moderate agitation
- 3 = mild agitation
- 4 = normal behavior
- 5 = mild calmness
- 6 = moderate calmness
- 7 = marked calmness
- 8 = deep sleep
- 9 = unarousable

4.2.4. Drug Likeability Scale

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

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

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

The Alzheimer's Disease Assessment Scale - Cognitive Subscale 12 (ADAS-Cog12) was developed in the 1980s to assess the level of cognitive dysfunction in AD. Although the ADAS-Cog12 was designed for people with AD, the ADAS-Cog12 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. The cognitive subscale of the original ADAS-Cog12 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.

4.2.6. Drug Likability Questionnaire

Subjects will also 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.

4.2.7. Pittsburgh Agitation Scale

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).

4.2.8. The Folstein Mini-Mental State Exam

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. Exhibit **5** provides an interpretation of MMSE scores. Subjects in this study will have score of 0 to 20 (moderate to severe) on the MMSE at Screening (see inclusion criterion #5). The MMSE is interpreted as shown below.

Exhibit 5. 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.

4.2.9. 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.

4.2.10. Katz Index

The Katz Index of Independence in Activities of Daily Living (Katz ADL) is a validated scale used to assess the level of independency in older adults by measuring an individual's ability to independently perform activities of daily living (Katz et al., 1970). The Katz ADL consists of 6 items representing the daily living functions of bathing, dressing, toileting, transferring, continence, and feeding. An individual's ability to perform activities in each of these 6 functional domains is rated as either 1 point for independence or 0 points for dependence (needing supervision, direction, assistance or total care). Higher scores on the Katz ADL mean greater independence in performing activities of daily living with the highest score of 6 meaning full independence, a score of 4 indicating moderate impairment in performing ADLs independently, and a score of 2 or lower indicating severe impairment in functioning with very limited to no ability to perform ADLs independently..

4.3. Efficacy endpoints

4.3.1. Primary endpoint

- The change from pre-dose in PEC total score at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose for the first treated episode of agitation.

4.3.2. Secondary efficacy endpoints

The secondary efficacy endpoints are as follows:

- The change from baseline in PAS at 2 hours post-dose for the first episode of agitation.
- The change from baseline in CGI-S at 2 hours post-dose for the first episode of agitation.
- The CGI-I score at 30 minutes, 1 hour, and 2 hours post-dose over all treated episodes of agitation.
- The change from baseline in ACES scores at 1, 2, 4, and 8 hours post-dose for the first episode of agitation.
- The frequency of treated episodes of agitation after the first treated episode.

4.4. Safety assessments

Safety will be assessed during the study by the monitoring and recording of adverse events (AEs), clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate measured as pulse, respiratory rate, and temperature), ECG, and physical examination findings.

4.4.1. Adverse events

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 relation 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.

4.4.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale that identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS Baseline/Screening

version will be conducted at Screening. The C-SSRS Since Last Visit version will be conducted 24 hours post-dosing and at discharge.

4.4.3. 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 (Exhibit 3).

4.4.4. Laboratory safety assessments

Exhibit 5 presents the laboratory tests that will be collected at the timepoints specified in the schedule of events (Exhibit 3).

Exhibit 6. Laboratory safety assessments

Hematology	Complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serum chemistry	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	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test*	Women of child-bearing potential only
Urine drug screen*	Cocaine, amphetamine, phencyclidine, benzodiazepines, marijuana. (Note: marijuana positive is allowed provided subject is not moderately to severely dependent, benzodiazepine positive are allowed if prescribed.)

*Conducted at Screening only

4.4.5. Vital signs

Resting vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (measured as pulse) will be measured after the subject has been in a recumbent position for at least five minutes at the timepoints specified in the schedule of events (Exhibit 3). Measurements should be made at least one minute apart using the same arm at each visit.

At indicated timepoints, orthostatic measurement of SBP, DBP, and heart rate will be measured after the subject has been standing for a total of five minutes. 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.

If the first measurement of vital signs (SBP, DBP, and pulse) shows SBP <90 mmHg, DBP <60 mmHg, or pulse <60 bpm, vital signs will be measured again in triplicate (same arm, separated by at least 1 minute).

4.4.6. Electrocardiogram (ECG)

A 12-lead ECG with rhythm strip will be performed at Screening, pre-dose (not required if Screening ECG is conducted on the day of dosing), 2 hours, 4 hours, and 24 hours post-dose.

4.4.7. Physical examinations

A standard physical examination will be performed at Screening. The examination 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.

Height and weight will be measured at Screening, and weight will be measured again on the day of discharge.

4.4.8. Concomitant medications

Concomitant medications will be reviewed and documented during the study.

4.5. Other assessments

4.5.1. EuroQoL-5 Dimensions-5 Level (EQ-5D-5L)

The EQ-5D-5L questionnaire is designed to measure health in terms of five dimensions of mobility, selfcare, usual activities, pain/discomfort and anxiety/depression on a 5-point scale (Herdman et al., 2011). The instrument will be administered to a caregiver for the subject by an interviewer

5. Statistical analyses

Statistical analyses will be performed using SAS® software version 9.4 or higher.

5.1. Statistical methodology

5.1.1. 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 provide 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.

Sample size criterion will not be met due to study closure.

5.1.2. Blinded sample size recalculation

A blinded sample size recalculation is planned when approximately 50% of the PEC total score data at 2 hours for the first treated episode are available. The standard deviation of the change from baseline in PEC total score will be computed at the 30 minute, 1 hour, and 2 hour timepoints. The standard deviations will be computed in the full dataset and not by treatment group to ensure that the blinding is maintained. The sample size will then be recalculated with the potential to adjust the sample size accordingly.

Sample size will not be recalculated due to study closure.

5.1.3. 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 patients in the Safety Population, classified as randomized.

5.1.4. General considerations

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.

5.1.5. Procedures for handling missing data

No imputation will be performed for missing data

5.2. Demographics and baseline characteristics

The following demographics and baseline characteristics will be presented in summary tables by treatment for the safety population: demographic characteristics (age, sex, race, ethnicity), weight, height, body mass index (BMI), Johns Hopkins Fall Risk Assessment and Katz Index.

5.3. Subject disposition

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

5.4. Efficacy analyses

Due to study closure, efficacy analysis calculations will not be conducted. Efficacy data will be summarized for the full analysis set (FAS) with descriptive statistics by treatment group.

Observed and change from pre-dose results at each specified timepoint will be presented for the PEC for the first treated episode and last treated episode, as well as the PAS, the CGI-S, the CGI-I and ACES for the first treated episode of agitation.

The frequency of treated episodes of agitation after the first treated episode will be summarized.

6. Safety and Tolerability analyses

Safety data analysis will be conducted on all subjects receiving at least 1 dose of study drug.

6.1. Adverse events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later coding system. Frequency tables will be presented by treatment groups summarizing:

- All treatment-emergent AEs
- All treatment-emergent AEs by severity
- All treatment-emergent treatment-related AEs

AE tables will be created for reporting of adverse events occurring within 24 hours of the first administration of BXCL501 and within 24 hours after any dose of BXCL501. An additional set of AE tables will be provided for adverse events recorded over the study period.

A listing specific to the reporting of the following adverse events of special interest will also be created: orthostatic hypotension, hypotension, bradycardia, sinus bradycardia, and somnolence (rated moderate by the investigator). This listing will present information across all administrations of BXCL501.

All serious treatment-emergent AEs and all AEs leading to study discontinuation will be listed.

6.2. Clinical laboratory evaluations, Physical Examination, Concomitant medications, Sublingual exam for local irritation

Laboratory results, physical examination results, concomitant medications, and sublingual exam results will be summarized in listings.

6.3. Vital signs

Vital signs will be summarized in listings.

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).

Abnormal postural changes in blood pressures will be summarized for each treatment group at each specified timepoint associated with the first administration of BXCL501 and across all scheduled study visits.

6.4. 12-lead electrocardiogram

ECG results will be summarized in listings. Frequency tabulation of the overall ECG results (normal, abnormal not clinically significant [NCS], and abnormal clinically significant [CS]) will be summarized (to include any emergent arrhythmias and determination of resolution) by each treatment group. These results will be summarized for the first dose and across all scheduled study visits. Conduction intervals including PR, QRS, QT (>450, >500ms) and QTc (>450, >500 ms) will be summarized and tabulated.

7. Additional assessments

The drug likability scale and likability questionnaire will be summarized in listings.

The C-SSRS will be summarized in listings at each time point including the responses to the individual items belonging to the suicidal ideation and suicidal behavior subscales.

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 and summarized with demographics.

The Katz Index of Independence in Activities of Daily Living (Katz ADL) is a validated scale used to assess the level of independency in older adults by measuring an individual's ability to independently perform activities of daily living (Katz et al., 1970). The assessment will be conducted at the Screening visit and summarized with demographics.

The MMSE will be administered at Screening, at the time of the first dose of BXCL501 or placebo, at Day 28, and at Day 84. The results will be summarized in listings with change from baseline.

The ADAS-Cog12 is administered at Screening and at Day 84. The results will be summarized descriptively at Screening and at Day 84. The change from baseline to Day 84 will also be summarized in listings.

The EQ-5D-5L questionnaire will be administered at Screening and at Day 84. Results will be summarized in listings.

Agitation behaviors, which are collected pre-dose and at 2 hours post-dose, will be summarized in a table for the first dose administration and also for all dose administrations in listings.

8. References

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