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

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10/25/2021

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PROTOCOL NUMBER:	BXCL501-203
STUDY PHASE:	Phase 2
IND NUMBER:	156685
PROTOCOL VERSION:	1
PROTOCOL DATE:	25-Oct-2021
SPONSORED BY:	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 Phone: PPD

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 BXCL501 FOR THE TREATMENT OF AGITATION ASSOCIATED WITH DEMENTIA

PROTOCOL NUMBER: BXCL501-203

PROTOCOL VERSION: 1

PROTOCOL DATE: 25-Oct-2021

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

STUDY PRODUCT: BXCL501

Sponsor Approval:

Date: 26-Oct-2021

Signature: DocuSigned by: PPD

PPD
Medical Monitor

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

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: BXCL501-203

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: BXCL501-203

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

Estimated number of study center(s): Multicenter, up to 20 sites in the US

Phase of development: Phase 2

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) that erodes quality of life, may result in harm to self and others, and may precipitate treatment escalation including hospitalization 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 medications 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 Subjects and increasing the need for physical restraint or seclusion (Allen et al., 2003) and all are associated with problematic side effects.

BXCL501 is designed as a self-administered, discrete, low-dose, orally dissolving sublingual or buccal film with mucoadhesive properties. It is expected that its administration in agitated subjects will lead to clinical reduction of agitation without excessive sedation or use of antipsychotics or intramuscular preparations. This double-blind, placebo-controlled study is planned to characterize the efficacy, safety, and tolerability of BXCL501 in Subjects with dementia.

Objectives:

Primary objective:

To describe the efficacy, safety and tolerability of single doses of BXCL501 in the treatment of acute agitation associated with dementia.

Key Secondary objective:

To describe the onset and magnitude of the effects on acute agitation associated with dementia of two doses of BXCL501 compared to placebo.

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Other secondary objectives:

1. Describe the duration of calming as measured by the Positive and Negative Syndrome Scale Excited Component (PEC), the Pittsburg Agitation Scale (PAS), and the Agitation-Calmness Evaluation Scale (ACES).
2. Describe the effects on agitation as measured by the Clinician Global Impression of Improvement scale (CGI-I).
3. Describe the PK and exposure of dexmedetomidine as delivered by sublingual BXCL501 dosing.

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 geriatric residents (65 years and older) with acute agitation associated with all forms of dementia (i.e., probably Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia) excluding Parkinson's-Related Dementia and Lewy Body Dementia.

At least 75 subjects will be enrolled and randomized 1:1:1 to receive a single film consisting of BXCL501 40 µg dose, BXCL501 60 µg dose, or matching placebo film. Subjects must reside in a residential care facility and must require at least moderate assistance with activities of daily living (e.g., bathing, dressing, and toileting). Moderate assistance can be generally defined as the patient requiring help more than just a light supportive touch. The patient can use his/her body in initiating activity but may be unable to initiate or perform a part of the activity safely. Subjects will remain in their domicile, where all study-related assessments and procedures will be performed under the supervision of qualified research staff. The staff at the care facility will continue to supervise and care for the subject. At the time of dosing, research staff will instruct the subjects on how to take the investigational product sublingually or buccally (behind the lower lip between the gum and lip), and that they should retain the investigational product in place until dissolved. The subject will self-administer the investigational product under the supervision of a trained staff member. Placement of the strip will be confirmed and documented. The buccal cavity will be examined for signs of irritation. Subjects will be allowed fluids as desired after at least 15 minutes after completion of dosing. The subject must be able to self-administer the film to participate in the study.

Up to 1 hour prior to dosing, blood pressure (BP), orthostatic BP, and adverse events (AEs) will be collected. If orthostatic hypotension (OH) is observed or if systolic blood pressure (SBP) is less than 110 mmHg, then the subject will be offered hydration, and dosing should be delayed until OH is resolved. After dosing, subjects will be encouraged to remain sitting or lying down for at least 2 hours. Study staff or subject's caregiver should remain with the subject for the first 2 hours after dosing to ensure subjects do not fall while monitoring the effect of dosing.

If agitation persists (defined by a PEC reduction <40%) after the 2-hour timepoint, investigators may choose to repeat dose if the criteria below are met. In the absence of safety concerns (see repeat dosing criteria below) the repeat dose will be 40 µg BXCL501 for both the 40 µg and 60 µg (active) treatment groups, or matching placebo for the placebo treatment group. The maximum number of repeat doses per subject is 1. This repeat dose cannot be administered until 2 or more hours have passed after the initial dose and after the collection of the 2 hour initial dose assessments. The repeat dose must occur within 12 hours of the initial dose and there must be documentation to support a PEC change from

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baseline of <40% (where baseline is PEC total score before initial first dose administered for the current agitation episode).

Two hours after the repeat dose is administered, assessments associated with the 2 hour timepoint are to be performed. If a timed assessment associated with the INTIAL dose occurs within 1 hour of the repeat dose assessment, then the post initial dose assessments do not need to be repeated. All remaining assessment timepoints are based off the time of the INITIAL dose.

In addition, a single PK sample associated with the repeat dose is to be collected 2.5 hours following a repeat dose. If this collection coincides with a collection associated with the initial dose, then only collect that one sample. All remaining PK timepoints are based on when the INITIAL dose was administered (see Table 3.1).

Repeat Dosing Criteria:

Subjects will not be permitted to receive a repeat dose of BXCL501 if any of the below criteria are met:

1. PEC reduction ≥40%
2. More than 12 hours elapse since first dose
3. Hypotension (BP ≤90/60 mmHg)
4. Bradycardia (heart rate ≤60 bpm)
5. Orthostasis (drop of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure upon standing)
6. Clinically significant AE

Efficacy and safety assessments will be conducted per schedule of events (Table 3.1). 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 with lorazepam 0.5-5 mg po/IM may be initiated at any time, preferably after the 4-hour assessments are completed.

Efficacy, safety, and tolerability will be measured throughout the treatment period at various timepoints. Please refer to Table 3.1 (Schedule of Events) for details.

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on the final study day or upon early termination. For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be stable and no longer of clinical concern.

Number of subjects (planned): At least 75 subjects will be enrolled and randomized at approximately 20 study sites in the United States. Subjects will be randomized 1:1:1.

Subjects:

Individuals with any form of dementia (i.e., probable Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia) other than Parkinson's-Related Dementia or Lewy Body Dementia who have a history of recent episodes of acute agitation (within 6 months or less of screening) are eligible.

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Subjects must require at least moderate assistance with activities of daily living (e.g., bathing and dressing). 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, subjects will be randomized to either BXCL501 40 µg dose, BXCL501 60 µg dose or placebo film in a 1:1:1 randomization ratio.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

1. Male and female subjects 65 years and older.
2. Individuals diagnosed with any form of dementia (i.e., probable Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia)
3. Subjects who have met DSM-5 criteria for dementia (major neurocognitive disorder) who have instances of acute psychomotor agitation.
4. History 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.
5. Subjects are expected to exhibit behaviors that are congruent with the International Psychogeriatric Association criterion for agitation representing a change from the subject's usual behavior.
6. Subjects who have a score of ≤16 on the Mini-Mental State Exam (MMSE) at Screening and Pre-Dose and require at least moderate assistance with activities of daily living (e.g., bathing, dressing, and toileting).
7. Subjects with a remote (>5 years) history of stroke may be included, regardless of size/location.
8. Subjects who read, understand, and provide written informed consent, or who have a legally authorized representative (LAR).
9. 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.
10. 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, 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 alone.
11. 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.
12. Subjects who have the capability to participate in the study and self-administer the investigational product.
13. Subjects who are on a stable concomitant medications regimen for the treatment of any concurrent conditions for at least one month prior to the screening visit.

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Exclusion Criteria

1. Subjects who have dementia associated with Parkinson's disease and/or Lewy Body Disease are excluded.
2. Subjects suffering from alcohol and/or substance abuse.
3. Subjects with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription illicit 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.
6. History of clinically significant syncope or syncopal attacks, orthostatic hypotension within the past 2 years, current evidence of hypovolemia, orthostatic hypotension (following 1, 3, and 5 minutes of standing, a ≥20 mmHg drop in SBP or ≥10 mmHg drop in DBP, or dizziness or lightheadedness), bradycardia, or baseline (pre-dose) measurements of heart rate <60 bpm, SBP <110 mmHg, or DBP <70 mmHg must be excluded.
7. 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 patient's participation in the study must be excluded.
8. 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.
9. Subjects who have received an investigational drug within 30 days prior to Screening must be excluded.
10. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine must be excluded, e.g., subjects with a history of allergic reactions to dexmedetomidine.
11. Subjects whose agitation is attributed to pain or infection, delirium, concomitant medications, environmental conditions, or another psychiatric condition or medical condition as determined by the investigator.
12. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study.
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.

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Randomization Criteria: (determined prior to dosing)

1. Subjects who score ≥14 on the PEC scale total score at Pre-Dose
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 PAS.

Test Product, Dose, and Mode of Administration: BXCL501 is a thin, solid-dose film formulation of dexmedetomidine, approximately 286 mm^2 in area, designed to dissolve in the sublingual or buccal space. Dosing delivers 40 µg or 60 µg sublingually or buccally.

Reference therapy, dosage and mode of Administration: Matching placebo films to be taken sublingually or buccally as described above.

Duration of Treatment: 1 day

Criteria for Evaluation:

Efficacy:

The effects of BXCL 501 on acute agitation will be assessed by the following scales: PEC, PAS, ACES, and CGI-I.

Efficacy assessment:

Primary Endpoint. The change in scores assessing acute agitation at 2 hours post-dose on the Positive and Negative Syndrome Scale – Excited Component (PEC) 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).

Secondary Endpoints. The anti-agitation effects of BXCL501 will also be assessed by examining the change from Baseline for assessments at 2 hours post-dose for each of the following scales:

- The Pittsburgh Agitation Scale (PAS) assesses agitation for individuals with dementia across four behavior groups: aberrant vocalizations, motor agitation, aggressiveness, and resisting care. Each behavior group is scored ranging from 0 (not present) to 4 (maximally present).
- Overall agitation and sedation will be evaluated with the Agitation-Calmness Evaluation Scale (ACES), where 1 indicates marked agitation; 2 - moderate agitation; 3 - mild agitation; 4 - normal behavior; 5 - mild calmness; 6 - moderate calmness; 7 - marked calmness; 8 - deep sleep; and 9 - unarousable.
- The overall clinical improvement in agitation in response to treatment will be measured by the CGI-I.

Safety and tolerability assessments: 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

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investigators. Vital signs including SBP, DBP, and HR 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.

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). Safety and tolerability assessments will be continued until the morning of Day 2 and Day 3 and will be repeated on Day 7 + 2 days.

Additional Assessments: Demographics, Medical and Psychiatric History, psychotic symptoms (PANSS), Smoking History, Prior and Concomitant Medication, Physical Examination, Pregnancy.

Pharmacokinetics: An attempt will be made to collect blood samples for PK plasma concentrations if study staff are able to procure a sample. PK sampling for plasma concentrations could occur at specified timepoints (30 minutes, 1 hour, 2, hours, 4 hours, 7-9 hours, 10-12 hours, and 24 hours post-dose).

Statistical Analysis:

General: The null and alternative hypotheses to be tested are stated as H_{01}: $\Delta_{BXCL501\_40} = \Delta_{PBO}$ and H_{A1}: $\Delta_{BXCL501\_40} \neq \Delta_{PBO}$ and H_{02}: $\Delta_{BXCL501\_60} = \Delta_{PBO}$ and H_{A2}: $\Delta_{BXCL501\_60} \neq \Delta_{PBO}$, where $\Delta_{BXCL501\_40}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 40 µg group, $\Delta_{BXCL501\_60}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 60 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 and set at 0.025. Conditional upon statistical significance at 2 hours of a given dose versus placebo at the 0.025 alpha-level, earlier time points will be tested hierarchically (each at alpha=0.025) to determine the earliest time point where statistical significance is reached for each dose versus placebo. Subjects will be classified according to randomized treatment.

Safety Analyses: Safety data analysis will be conducted on all subjects receiving at least 1 dose of study drug, with subjects classified according to the drug actually received. 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 (Med DRA) 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.

Sample Size Determination: [redacted]
CCI [redacted]

Table 3.1: Schedule of Events

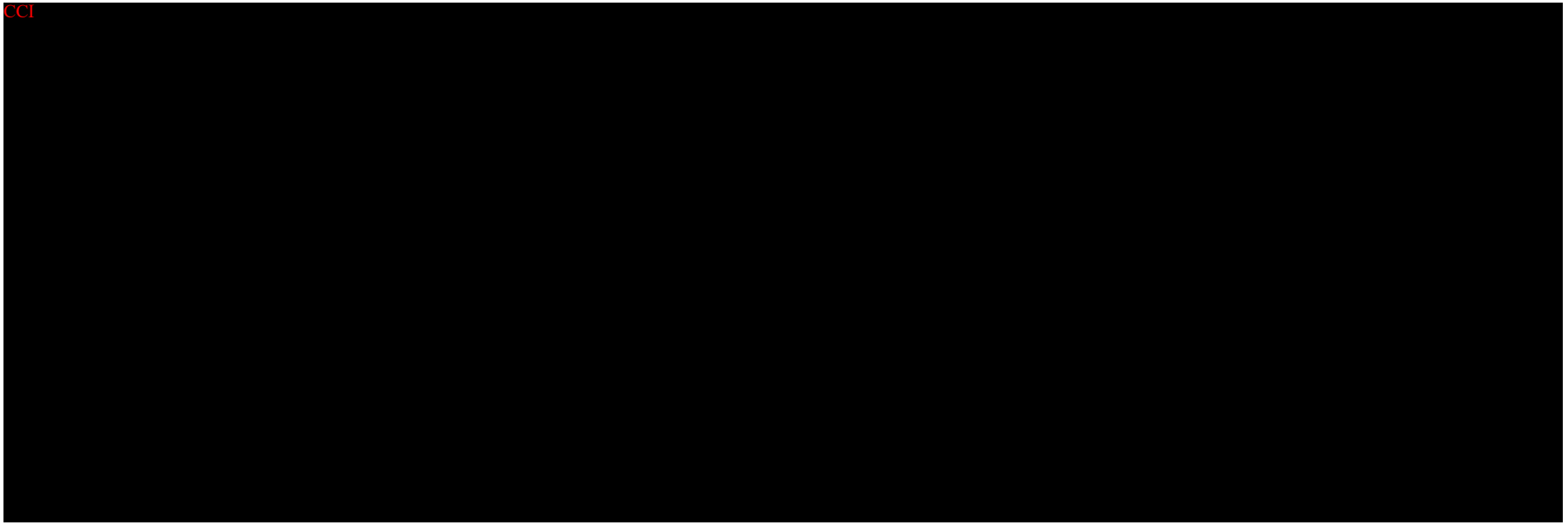
Procedures	Timepoints												
	Screening[1]	Pre-Dose[2]	Day 1, Treatment Evaluation								Day 2 Follow-Up (+1 day)	Day 3 (+1 day)	Day 7 (+2 days)
			15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr (-9/+12 hr)		End of Study
Informed consent	X												
Medical history[3]	X												
Demographics	X												
Weight	X												
Height	X												
Mini-Mental State Exam	X	X									X		
Physical exam	X										X		
Safety laboratory assessments[4]	X											X	
UDS[5]	X												
UTI and pregnancy	X												
Johns Hopkins Fall Risk Assessment[6]	X												
ECG with rhythm strip[7]	X	X				X			X		X	X	X
Pulse oximetry		X		X	X	X	X	X	X		X		
Resting vital signs[8]	X	X		X	X	X	X	X	X		X	X	X
Orthostatic vital signs[9]	X	X		X	X	X	X	X	X		X	X	X
Inclusion/Exclusion criteria	X	X											
Randomization		X											
Study drug administration[10]		X											
PEC	X	X	X	X	X	X	X		X	X	X	X	
PAS	X	X		X	X	X	X		X	X	X	X	
ACES		X			X	X	X		X	X	X		
CGI-S (agitation)		X											

Procedures	Timepoints												
	Screening[1]	Pre-Dose[2]	Day 1, Treatment Evaluation								Day 2 Follow-Up (+1 day)	Day 3 (+1 day)	Day 7 (+2 days)
			15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr (-9/+12 hr)		End of Study
CGI-I (change in agitation)				X	X	X	X		X	X	X		
C-SSRS	X										X		
Buccal (SL) assessment for local irritation		X		X		X	X				X		
PK sampling[11]				X	X	X*	X		X	X	X		
Concomitant medications	X	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

Abbreviations: ACES = Agitation-Calmness Evaluation Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PAS = Pittsburgh Agitation Scale; PEC = Positive and Negative Syndrome Scale – Excited Component; PK = pharmacokinetic; PRN = as needed; SL = sublingual; UDS = urinary drug screen; UTI = urinary tract infection

Notes to the Schedule of Events:

CCI



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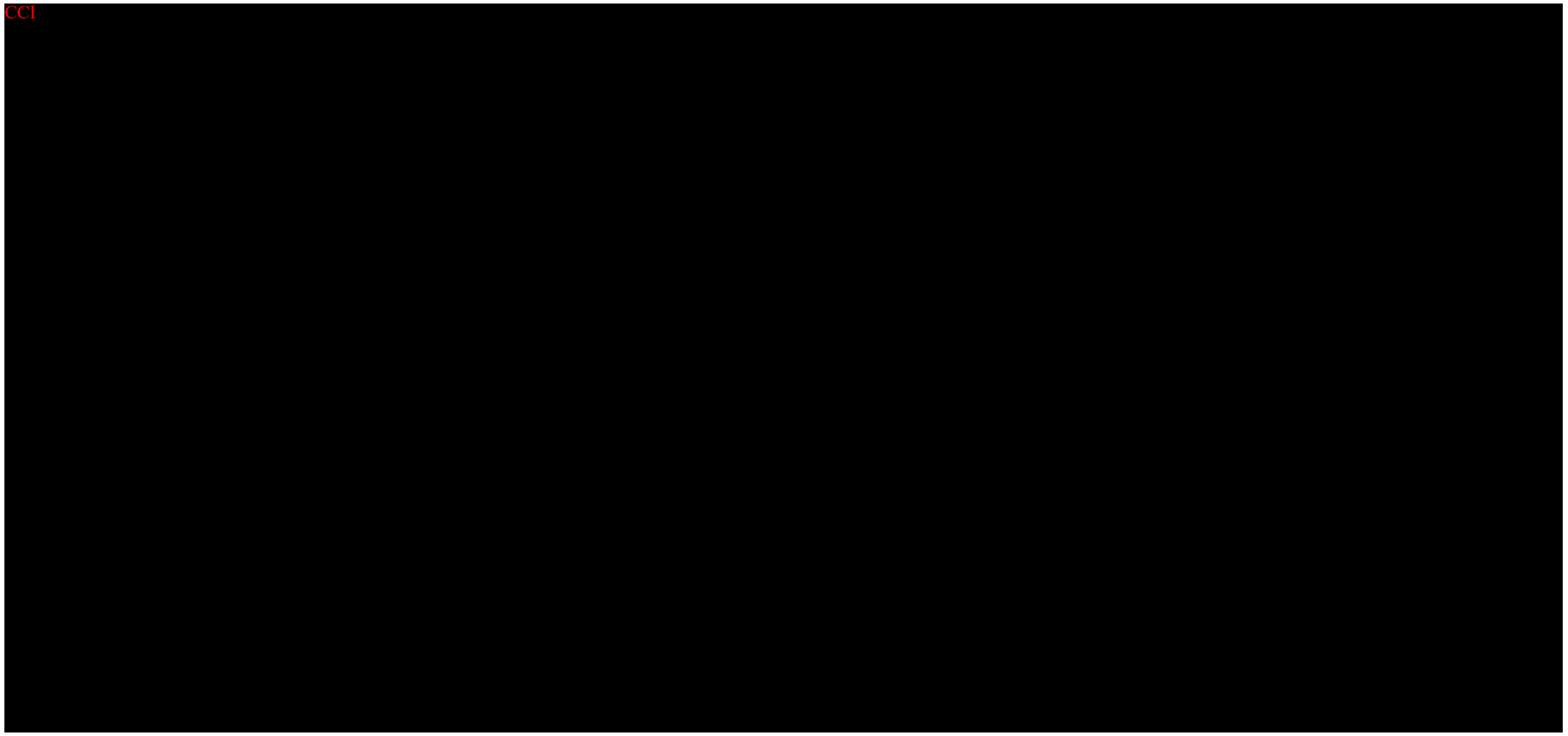

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4.1. LIST OF TABLES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse event
BP	Blood pressure
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CMAI	Modified Cohen-Mansfield Agitation
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
hr	Hour
ICH	International Council for Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LAR	Legally authorized representative
min	Minutes
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
MMSE	Mini-Mental State Exam
PANSS-EC/PEC	Positive and Negative Syndrome Scale/ Positive and Negative Syndrome Scale – Excited Component
PAS	Pittsburgh Agitation Scale
PK	Pharmacokinetic
po	Oral/by mouth
PP	Per Protocol
RASS	Richmond Agitation Sedation Scale

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SL	Sublingual
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) that erodes quality of life, may result in harm to self and others, and may precipitate treatment escalation including hospitalization 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 medications 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 Subjects and increasing the need for physical restraint or seclusion (Allen et al., 2003) and all are associated with problematic side effects.

BXCL501 is designed as a self-administered, discrete, low-dose, sublingual or buccal film with mucoadhesive properties. It is therefore expected that its administration in agitated Subjects will lead to clinical reduction of agitation without excessive sedation or use of antipsychotics or intramuscular preparations. This double-blind, placebo-controlled study is planned to characterize the efficacy, safety, and tolerability of BXCL501in Subjects with dementia.

Dexmedetomidine is currently approved in the United States (US) as the intravenous injectable formulation, Precedex® (Precedex US Package Insert, 2016), for acute procedural and Intensive Care Unit sedation.

6.2. Description of BXCL501

BXCL501 is a sublingual film comprised of dexmedetomidine CCI [redacted] the active pharmaceutical ingredient and the following inactive ingredients: [redacted]
CCI [redacted].

Packaged films must be stored at room temperature (20- 25°C) 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 (National Center for Biotechnology Information, 2021).

Since the pharmacologic effects of intravenous (IV) dexmedetomidine have been characterized, BioXcel sought to evaluate various dexmedetomidine metrics following administration by the sublingual (SL) or buccal 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 SL administration of BXCL501 in animal models produced 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 study medication: 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.

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 BXCL 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. CCI

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6.4.4. Phase 1b/I2 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 dose BXCL501 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 Intent-to-Treat (ITT) population. All subjects completed the study.

Efficacy

[redacted]

[redacted]

7. OBJECTIVES

7.1. Primary

The primary objective of this study is to:

Describe the efficacy, safety and tolerability of single doses of BXCL501 in the treatment of acute agitation associated with dementia.

7.2. Key Secondary

The key secondary objective of this study is to:

Describe the onset and magnitude of the effects on acute agitation associated with dementia of two doses of BXCL501 compared to placebo.

7.3. Other Secondary

Other secondary objectives of this study are to:

1. Describe the duration of calming as measured by the Positive and Negative Syndrome Scale Excited Component (PEC), the Pittsburg Agitation Scale (PAS), and the Agitation-Calmness Evaluation Scale (ACES).
2. Describe the effects on agitation as measured by the Clinician Global Impression of Improvement scale (CGI-I).
3. Describe the PK and exposure of dexmedetomidine as delivered by sublingual BXCL501 dosing.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This study (BXCL501-203) 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 geriatric residents (65 years and older) with acute agitation associated with all forms of dementia (i.e., probably Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia) excluding Parkinson's-Related Dementia and Lewy Body Dementia.

At least 75 subjects will be enrolled and randomized 1:1:1 to receive a single film consisting of BXCL501 40 µg dose, BXCL501 60 µg dose, or matching placebo film. Subjects must reside in a residential care facility and must require at least moderate assistance with activities of daily living (e.g., bathing, dressing, and toileting). Moderate assistance can be generally defined as the patient requiring help more than just a light supportive touch. The patient can use his/her body in initiating activity but may be unable to initiate or perform a part of the activity safely. Subjects will remain in their domicile, where all study-related assessments and procedures will be performed under the supervision of qualified research staff. The staff at the care facility will continue to supervise and care for the subject. At the time of dosing, research staff will instruct the subjects on how to take the investigational product sublingually or buccally (behind the lower lip between the gum and lip), and that they should retain the investigational product in place until dissolved. The subject will self-administer the investigational product under the supervision of a trained staff member. Placement of the strip will be confirmed and documented. The buccal cavity will be examined for signs of irritation. Subjects will be allowed fluids as desired at least 15 minutes after completion of dosing. The subject must be able to self-administer the film to participate in the study.

Up to 1 hour prior to dosing, blood pressure (BP), orthostatic BP, and adverse events (AEs) will be collected. If orthostatic hypotension (OH) is observed or if systolic blood pressure (SBP) is less than 110 mmHg, then the subject will be offered hydration, and dosing should be delayed until OH is resolved. After dosing, subjects will be encouraged to remain sitting or lying down for at least 2 hours. Study staff or subject's caregiver should remain with the subject for the first 2 hours after dosing to ensure subjects do not fall while monitoring the effect of dosing.

If agitation persists (defined by a PEC reduction <40%) after the 2-hour timepoint, investigators may choose to repeat dose if the criteria below are met. In the absence of safety concerns (see repeat dosing criteria below) the repeat dose will be 40 µg BXCL501 for both the 40 µg and 60 µg (active) treatment groups, or matching placebo for the placebo treatment group. The maximum number of repeat doses per subject is 1. This repeat dose cannot be administered until 2 or more hours have passed after the initial dose and after the collection of the 2 hour initial dose assessments. The repeat dose must occur within 12 hours of the initial dose and there must be documentation to support a PEC change from baseline of <40% (where baseline is PEC total score before initial first dose administered for the current agitation episode).

Two hours after the repeat dose is administered, assessments associated with the 2 hour timepoint are to be performed. If a timed assessment associated with the INTIAL dose occurs within 1 hour of the repeat dose assessment, then the post initial dose assessments do not need to be repeated. All remaining assessment timepoints are based off the time of the INITIAL dose.

In addition, a single PK sample associated with the repeat dose is to be collected 2.5 hours following a repeat dose. If this collection coincides with a collection associated with the initial dose, then only collect that one sample. All remaining PK timepoints are based on when the INITIAL dose was administered (see Table 3.1).

Repeat Dosing Criteria:

Subjects will not be permitted to receive a repeat dose of BXCL501 if any of the below criteria are met:

1. PEC reduction ≥40%
2. More than 12 hours elapse since first dose
3. Hypotension (BP ≤90/60 mmHg)
4. Bradycardia (heart rate ≤60 bpm)
5. Orthostasis (drop of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure upon standing)
6. Clinically significant AE

8.2. Stopping Criterion

If a treatment arm has 2 drug-treated patients experiencing syncope or a single syncope related fall, dosing will be suspended pending blinded review of the patient data.

8.3. Study Sites

The study will take place at approximately 20 sites in the US.

9. SUBJECT POPULATION

9.1. Selection of Study Population

Individuals with any form of dementia (i.e., probable Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia) other than Parkinson's-Related Dementia or Lewy Body Dementia who have a history of recent episodes of acute agitation (within 6 months or less of screening) are eligible. Subjects must require at least moderate assistance with activities of daily living (e.g., bathing and dressing). 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. Individuals diagnosed with any form of dementia (i.e., probable Alzheimer's Disease; vascular dementia; mixed; frontotemporal dementia).
3. Subjects who have met DSM-5 criteria for dementia (major neurocognitive disorder) who have instances of acute psychomotor agitation.
4. History 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.
5. Subjects are expected to exhibit behaviors that are congruent with the International Psychogeriatric Association criterion for agitation representing a change from the subject's usual behavior.
6. Subjects who have a score of ≤16 on the Mini-Mental State Exam (MMSE) at Screening and Pre-Dose and require at least moderate assistance with activities of daily living (e.g., bathing, dressing, and toileting).
7. Subjects with a remote (>5 years) history of stroke may be included, regardless of size/location.
8. Subjects who read, understand, and provide written informed consent, or who have a legally authorized representative (LAR).
9. 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.
10. 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, 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 alone.

11. 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.
12. Subjects who have the capability to participate in the study and self-administer the investigational product.
13. Subjects who are on a stable concomitant medications regimen for the treatment of any concurrent conditions for at least one month prior to the Screening Visit.

9.1.2. Exclusion Criteria

1. Subjects who have dementia associated with Parkinson's disease and/or Lewy Body Disease are excluded.
2. Subjects suffering from alcohol and/or substance abuse.
3. Subjects with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription illicit 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.
6. History of clinically significant syncope or syncopal attacks, orthostatic hypotension within the past 2 years, current evidence of hypovolemia, orthostatic hypotension (following 1, 3, and 5 minutes of standing, a ≥20 mmHg drop in SBP or ≥10 mmHg drop in DBP, or dizziness or lightheadedness), bradycardia, or baseline (pre-dose) measurements of heart rate <60 bpm, SBP <110 mmHg, or DBP <70 mmHg must be excluded.
7. 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 patient's participation in the study must be excluded.
8. 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.
9. Subjects who have received an investigational drug within 30 days prior to Screening must be excluded.
10. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine must be excluded, e.g., subjects with a history of allergic reactions to dexmedetomidine.
11. Subjects whose agitation is attributed to pain or infection, delirium, concomitant medications, environmental conditions, or another psychiatric or medical condition as determined by the investigator.

12. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study.
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.

9.1.3. Randomization Criteria (determined prior to dosing)

1. Subjects who score ≥14 on the PEC scale total score at Pre-Dose.
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 PAS.

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 unacceptable 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 assessments, patients will be randomized to BXCL501 or placebo film.

Subjects will be randomized 1:1:1 to receive a single film consisting of BXCL501 40 µg dose, BXCL501 60 µg dose, or matching placebo film.

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 or buccal space. Dosing delivers 40 µg or 60 µg sublingually or buccally.

10.3. Treatment Administration

At the time of dosing, unblinded research staff will instruct the subjects on how to take the investigational product sublingually or buccally (behind the lower lip between the gum and lip), and that they should retain the investigational product in place until dissolved. The subject will self-administer the investigational product under the supervision of a trained unblinded staff member. Placement of the strip will be confirmed and documented. The buccal cavity will be examined for signs of irritation by the unblinded staff member. Subjects will be allowed fluids as desired at least 15 minutes after completion of dosing. The subject must be able to self-administer the film to participate in the study.

10.4. Storage

BXCL501 packaged films must be stored at room temperature (20-25°C with allowed excursion of 15-30°C). 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 United States Food and Drug Administration (FDA) Form 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 Form 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 designated study staff will be blinded to study treatment. An unblinded pharmacist will be responsible for the dispensation of study medication to the subject and the overall accountability of the investigational product. 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 or project manager 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 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 (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.

The highest proposed total daily dose in the current study is 100 µg (maximum of 1 repeat dose of 40 µg for both the 40 µg and 60 µg treatment groups), but the starting dose is only 40 µg, which provides an adequate safety margin if the PK, safety and/or tolerability is substantially different in the dementia population compared to the schizophrenic and bipolar populations.

As such, the sponsor decided to explore efficacy and safety of a BXCL501 40 µg dose cohort in this study (BXCL501-201) as an intermediate dose between BXCL501 30 µg and 60 µg.

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 6.4.1, respectively).

10.9. Treatment Compliance

Drug accountability will be performed by an unblinded pharmacist/designated study staff member. 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 study medication may be given at the discretion of the investigator.

10.10.1. Permitted Therapies

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 with lorazepam po/IM 0.5-5 mg may be initiated as a standard of care treatment for acute agitation. 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

Lorazepam or other benzodiazepines may be administered for insomnia. Administration may not occur sooner than 4 hours after dosing of the investigational product and the indication (insomnia) must be clearly recorded in the CRF and source documents.

10.10.2. Prohibited Therapies

A list of prohibited medications 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, at the time of randomization 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) and assent as applicable, before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

All subjects will follow the Schedule of Events provided in Table 3.1.

11.1. Screening (within 45 days before the first dose of investigational product)

The following procedures will be performed at Screening and may be conducted over more than one day during the Screening period (refer to the Schedule of Events Table 3.1):

- Obtain written informed consent from subject or LAR, and assent 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)
- UDS (note: UDS will be re-collected if more than 21 days have passed since screening)
- UTI and pregnancy
- Johns Hopkins Fall Risk Assessment
- ECG with rhythm strip
- MMSE
- PEC
- PAS
- C-SSRS

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 once at the discretion of the investigator.

11.2. Pre-Dose (90 minutes before the first dose of investigational product)

The following procedures will be performed at Pre-Dose:

- Review inclusion and exclusion criteria
- Record resting and orthostatic vital signs
- Record concomitant medication use
- 12-lead ECG with rhythm strip
- Pulse oximetry
- MMSE
- PEC
- PAS
- CGI-S
- C-SSRS
- Buccal (SL) assessment
- Randomization

11.3. Day 1, Treatment Evaluation (15 minutes to 12 hours post-dose)

Upon completion of the pre-randomization procedures, the subject will be randomized to study treatment (BXCL501 or placebo SL film) and the following procedures will be performed (refer to the Schedule of Events Table 3.1 for specific time points):

- Record resting and orthostatic vital signs
- 12-lead ECG with rhythm strip
- Pulse oximetry
- PEC
- PAS
- ACES
- Collect plasma samples for PK analysis. A sample may not be collected if the physician in charge of the patient indicates in the source documents that the patient is in a mental state that is not conducive to PK sample collection and record the PEC score at the time of proposed sample collection.
- CGI-I
- Buccal (SL) assessment
- Record concomitant medication use
- Assess and record AEs

11.4. Day 2/Follow-up (+1 day)

The following procedures will be performed on Day 2/Follow-up:

- Record resting and orthostatic vital signs
- 12-lead ECG with rhythm strip
- Physical exam
- Pulse oximetry
- MMSE
- PEC
- PAS
- ACES
- CGI-I
- C-SSRS
- Plasma sample for PK analysis at 24 hours (±1 hour window)
- Buccal (SL) assessment
- Record concomitant medication use
- Assess and record AEs

11.5. Day 3 (+1 day)

The following procedures will be performed on Day 3:

- Record resting and orthostatic vital signs
- 12-lead ECG with rhythm strip
- PEC
- PAS
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Record concomitant medication use
- Assess and record AEs

11.6. Day 7 (+2 Days): End of Study

The following procedures will be performed on Day 7 + 2 days:

- Record resting and orthostatic vital signs
- 12-lead ECG with rhythm strip
- Record concomitant medication use
- Assess and record AEs

12. STUDY ASSESSMENTS

12.1. Efficacy

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

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 et al., 2011).

12.1.2. 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).

12.1.3. Pittsburg Agitation Scale (PAS)

The Pittsburg 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, and resisting care (Rosen et al., 1994).

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.

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

Drug response on agitation will be evaluated by the Clinical Global Impressions – Improvement (CGI-I) which is performed after dosing and evaluated relative to pre-dose baseline agitation.

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

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

12.2.1. MMSE

The Folstein Mini-Mental State Examination (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 ≤16 on the MMSE at Screening and Pre-Dose (see inclusion criterion #6).

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.

12.3. Pharmacokinetics

Blood samples (4 mL) for PK analysis will be collected at timepoints including 0.5, 1, 2, 4, 7-9, 10-12, and 24 hours after first dose. 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) 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 except for the 24-hour post-dose collection, which will have a window of ±1 hour. All PK sampling will occur only after all other assessments at that timepoint are conducted (Table 3.1).

For each subject, the total amount of blood drawn for PK analyses will be 28 mLs (4 mLs x 7 collections [at 0.5, 1, 2, 4, 7-9, 10-12, and 24 hours after the first dose]). However, for subjects who receive a repeat dose, an extra PK blood sample (4 mL) will be collected at 2.5 hours post the first dose in addition to the other timepoints.

In addition, approximately 15 mL of blood will be collected at pre-treatment and approximately 15 mL of blood will be collected at Day 3 for clinical laboratory testing. The total volume of blood collected during the study is expected to be approximately 60 mL.

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. 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.
- The time elapsed from collection of the blood sample to completion of centrifugation should be no more than 60 minutes.

12.3.2. Sample Storage

Plasma samples will be placed in a storage freezer at -70°C (± 12°C) or on dry ice within 120 minutes of the blood collection. Samples should be placed in a -70°C (± 12°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 are 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:

CCI [redacted]
[redacted]
[redacted]
Tel: PPD
Cell: PPD

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, and HR 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.

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). Safety and tolerability assessments will be continued until the morning of Day 2 and Day 3 and will be repeated on Day 7 + 2 days (see Table 3.1).

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 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. Adverse events and SAEs will be collected from the time of the first dose of study medication through the Day 7 (End of Study) or Early Discontinuation visit.

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 from any data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) 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. The latest version of the Medical Dictionary for Regulatory Activities 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 the medical monitor within 24 hours of first becoming aware of the event by telephone. 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, and any actions taken

Within 24 hours of the initial notification, the investigator must e-mail a written SAE report form to the medical monitor/Safety team. 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).

The following contact information is to be used for SAE reporting:

Cognitive Research Corporation SAE mailbox: PPD

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 (https://www.hopkinsmedicine.org/institute_nursing/models_tools/fall_risk.html).

12.5.3. C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo et al., 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.

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 Table 3.1. Laboratory assessments will be performed by local laboratories.

Hematology:	Consists of 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	
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)

12.5.5. Vital Signs

Resting vital signs, including SBP, DBP, 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 timepoints specified in the schedule of events (Table 3.1). Measurements should be made at least 1 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** 5 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 the following, vital signs will be measured again in triplicate (same arm, separated by at least 1 minute) for:

- SBP <90 mmHg
- DBP <60 mmHg
- Pulse <60 bpm

12.5.6. Electrocardiogram

A 12-lead ECG with rhythm strip will be performed at Screening, Pre-dose, at 2, 8, and 24 hours post-dose, and on Day 3 and Day 7.

12.5.7. Physical Examination

A standard physical examination will be performed at Screening and at 24 hours post-dose (Day 2). 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.

12.5.8. Concomitant Medications

Concomitant medications will be reviewed and documented each day during the study.

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.

The null and alternative hypotheses to be tested are stated as H01: ΔBXCL501_40 = ΔPBO and HA1: ΔBXCL501_40 ≠ ΔPBO and H02: ΔBXCL501_60 = ΔPBO and HA2: ΔBXCL501_60 ≠ ΔPBO, where ΔBXCL501_40 denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 40 µg group, ΔBXCL501_60 denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 60 µg group, and ΔPBO 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 and set at 0.025. Conditional upon statistical significance at 2 hours of a given dose versus placebo at the 0.025 alpha-level, earlier time points will be tested hierarchically (each at alpha=0.025) to determine the earliest time point where statistical significance is reached for each dose versus placebo. Subjects will be classified according to randomized treatment.

13.2. Analysis Populations

The following analysis populations are planned:

- Safety Population: All subjects who receive study drug, according to the treatment received.
- Intent to treat (ITT) Population: All subjects in the Safety Population, analyzed as randomized.
- Per Protocol (PP) Population: All subjects in the ITT Population with no major protocol deviations likely to impact inference. Per Protocol analyses may not be conducted if there are not sufficient protocol deviations deemed to impact analysis. If subjects receive treatment other than to which they were randomized, they will be included in a PP analysis as treated (barring protocol deviations sufficient to exclude them for other reasons). The PP population will be finalized prior to breaking the blind.

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 medication. 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

The ITT population will be analyzed and consist of all patients who take any study medication and who had both baseline and at least 1 efficacy assessment after dosing. Observations recorded after use of rescue medication will be censored (considered missing).

13.3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in PEC total score at 2 hours post-dose.

PEC total scores at earlier time points will be tested hierarchically to determine earliest onset of action, conditional upon the significance of differences between BXCL501 40 µg and 60 µg versus placebo at 2 hours. Irrespective, nominal significance levels will be reported.

13.3.2.2. Secondary Efficacy Endpoints

The anti-agitation effects of BXCL501 will also be assessed by examining the change from Baseline for assessments at 2 hours post-dose for each of the following scales: PAS, ACES, and CGI-I.

13.3.3. Safety Analyses

Safety data analysis will be conducted on all subjects receiving at least 1 dose of study drug (Safety Population), with subjects classified according to the drug actually received. 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 (Med DRA) 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.

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).

Safety and tolerability assessments will be continued until the morning of Day 2 and Day 3 and will be repeated on Day 7 + 2 days.

13.3.4. Pharmacokinetic Analyses

An attempt will be made to collect PK plasma concentrations if study staff are able to procure a sample. Pharmacokinetic sampling of plasma concentrations could occur at specified timepoints (30 minutes, 1 hour, 2, hours, 4 hours, 7-9 hours, 10-12 hours, and 24 hours post-dose).

A separate SAP for PK analyses will be prepared for the study and will be finalized prior to database lock. Data from subjects who participated in the study will be included in the PK analysis. Subjects with missing sample concentrations will be included in the PK analyses provided their PK parameters can be adequately characterized based upon the remaining data.

Deviation from procedures described in this protocol that impact the quality of data required to meet the objectives of the study will be documented and may result in exclusion of PK data from the analyses for a subject. This includes any deviations or events that would invalidate the evaluation of the PK. Examples of deviations and events which could result in exclusion of PK data from the analyses include emesis after dosing (within the predetermined time), sample processing, or assay errors that lead to inaccurate bioanalytical results. Other deviations or events, which do not disqualify data from analyses, may require minor adjustments to calculations. If these occur, data analyses will be adjusted and documented accordingly such that conclusions are not biased. An example of such an event includes, but is not limited to, minor deviations between the actual and scheduled time of sample collection.

All PK parameters will be calculated using non-compartmental analysis using WinNonlin. Actual sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean plasma concentrations for graphical displays.

Other PK analyses, including using population pharmacokinetic methods, may be performed as appropriate.

13.4. Sample Size Determination

[redacted]
CCI
[redacted]

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(R2) 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 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.

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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