A PHASE Ib/II, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ASCENDING DOSE FINDING, EFFICACY, PHARMACOKINETIC AND SAFETY STUDY OF BXCL501 IN AGITATION ASSOCIATED WITH DEMENTIA

NCT04251910

02/04/2021

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PROTOCOL NUMBER:	BXCL501-103
STUDY PHASE:	Phase Ib/II
IND NUMBER:	140184
PROTOCOL VERSION:	7
ORIGINAL PROTOCOL DATE:	05 Nov 2019
AMENDMENT 1 DATE:	20 Nov 2019
AMENDMENT 2 DATE:	07 Dec 2019
AMENDMENT 3 DATE:	15 Jul 2020
AMENDMENT 4 DATE:	03 Sep 2020
AMENDMENT 5 DATE:	22 Oct 2020
AMENDMENT 6 DATE:	04 Feb 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 PHASE Ib/II, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ASCENDING DOSE FINDING, EFFICACY, PHARMACOKINETIC AND SAFETY STUDY OF BXCL501 IN AGITATION ASSOCIATED WITH DEMENTIA

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SPONSOR	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 USA
STUDY PRODUCT	BXCL501

Sponsor Approval:

Date: 2/4/2021

Signature: PPD

PPD, PPD

Medical Monitor

1. PROCEDURES IN CASE OF EMERGENCY

Table 1.1: Sponsor/CRO Contact Information

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

2. INVESTIGATOR AGREEMENT

PROTOCOL TITLE: A PHASE Ib/II, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ASCENDING DOSE FINDING, EFFICACY, PHARMACOKINETIC AND SAFETY STUDY OF BXCL501 IN AGITATION ASSOCIATED WITH DEMENTIA

PROTOCOL NUMBER: BXCL501-103

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: BXCL501-103

Title of study: A Phase Ib/II, Multicenter, Randomized, Double Blind, Placebo Controlled, Ascending Dose Finding, Efficacy, Pharmacokinetic and Safety Study of BXCL501 in Agitation associated with Dementia

Estimated number of study center(s): Multicenter, approximately 4 sites in the US

Phase of development: Ib/II

Rationale:

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

BXCL501 is designed as a self-administered, discrete, low-dose, sublingual film with mucoadhesive properties. It is therefore expected that its administration in agitated patients will lead to clinical calming without excessive sedation or use of antipsychotics or intramuscular preparations. A double-blind, placebo-controlled, ascending-dose study, in patients with dementia is planned to characterize the efficacy, pharmacokinetics (PK), safety, and tolerability of BXCL501 vs. placebo. This study will also support the determination of the dosage strengths that may be carried forward into subsequent clinical trials.

Objectives:

Primary objective:

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

Secondary objectives:

1. Describe the onset and magnitude of calming effects of different doses of BXCL501 on symptoms of acute agitation associated with dementia compared to placebo.

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2. Describe the duration of calming as measured by the Positive and Negative Syndrome Scale Excited Component (PEC) and the Agitation-Calmness Evaluation Scale (ACES).
3. Describe the tolerability and safety profile of BXCL501, as determined by adverse events (AEs) and vital signs vs. placebo.
4. Describe clinical effects as measured by the Clinician Global Impression of Severity scale (CGI-S) to assess agitation and then Improvement (CGI-I) after drug administration.
5. Describe the frequency of agitation using the Cohen Mansfield Agitation Inventory (CMAI) at baseline and 2 hours post-dose.
6. Determine the approximate dissolution time of BXCL501 films in the sublingual space.
7. Assess the local tolerability via buccal examination after dosing BXCL501 film.
8. Describe the PK and exposure of dexmedetomidine as delivered by sublingual BXCL501 dosing.
9. Part B: Describe the duration of calming as measured by the 3 supplementary items of the PANSS.

Study Design:

This is a Phase 1b/2, multicenter, randomized, double-blind, placebo-controlled, ascending dose study assessing efficacy, PK, safety, and tolerability of BXCL501 in adult (65 years and older) males and females with acute agitation associated with all forms of dementia. Evaluations of 3 doses are planned.

Subjects will be assigned to one of 3 dose cohorts, Cohort 1, Cohort 2, and Cohort 3, and will be randomized within their cohort to receive a single 30 µg (Cohort 1), 60 µg (Cohort 2), or 90 µg (Cohort 3) dose, respectively, of BXCL501 or placebo.

Subjects assigned to Cohort 3 will participate in a 1-week safety observation before being randomized. During this 1-week safety observation period, subjects will receive in-patient safety assessments to evaluate their risk for falling and syncope with twice daily blood pressure (BP) and orthostatic BP measurements, and recording of instances of falling and syncope. After the conclusion of the 1-week safety observation, subjects in Cohort 3 will complete the Screening visit and, if eligible, be randomized to either BXCL501 or placebo.

Part B procedures are the same as Cohorts 1 and 2 as outlined in the Schedule of Events (Table 3.1).

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In Part B a total of 46 subjects will be randomized 1:1 to receive BXCL501 40 µg or matching placebo film. This is an adaptive design, as doses selected for testing may be different from these, based upon safety reviews. Doses lower or higher may be chosen to test, up to 180 µg, and additional subjects may be added to a cohort. BXCL501 films may be divided in half if needed to deliver half-dose strengths. Except for Cohort 1, each subsequent dose-level cohort will be authorized after a safety review of the previous dosing cohort. Up to 1 hour prior to dosing, BP, orthostatic BP, and AEs will be collected. If orthostatic hypotension (OH) is observed or if systolic blood pressure (SBP) <110 mmHg, then the subject will be hydrated and dosing should be delayed until OH is resolved. Every effort will be made to keep the subject sitting or lying down for at least 2 hours after dosing. Dosing may be repeated for lack of efficacy, provided the first dose was well tolerated and the patient remains safe. If necessary, dosing may be repeated up to a total of 2 repeat doses for all cohorts (except Cohort 3, which can only be re-dosed 1 time) at 2 hours post-first dose, but only after the 2 hours post-first dose assessments are conducted and only within the first 12 hours post-first dose. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (SBP/diastolic blood pressure [DBP] must be greater than 90/60), and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of 20 points in either SBP or DBP) or if they are experiencing an AE. BXCL501 or placebo film will be self-administered sublingually by the patient under the supervision of an unblinded staff member who will not participate in evaluation of safety or efficacy. If the patient is unable to self-administer the drug, delegated personnel can do so. The drug film will be retained in the sublingual cavity until dissolved. There will be an evaluation to determine the time to dissolution of the film. Participants will also be evaluated for buccal irritation around the area where the films are placed. Participants will be allowed fluids as desired at least 15 minutes after completion of dosing. After completion of the lowest dose cohort (Cohort 1, 30 µg), a safety and tolerability review will be done by the Principal Investigator (PI) and BioXcel medical monitor. At dose escalation meetings, safety and tolerability data will be reviewed to determine the next dose to be tested. Pharmacokinetic data will be reviewed as it becomes available. A safety review will also be conducted in the event of a serious adverse event (SAE). Should the patient's situation warrant it, standard of care treatment may be initiated, preferably after the 4 hour assessments are completed. Analysis of the 30 and 60 µg cohorts revealed both doses were well tolerated with the 60 µg dose demonstrating efficacy vs. placebo on each independent measure of agitation. Although not reaching statistical significance, the 30 µg dose changes paralleled the statistically significant reductions in agitation observed for the 60 µg dose group, with a numerical improvement versus placebo on the PEC and PAS ratings over 8 hours.

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The objective of Part B is to test a dose of 40 µg vs placebo as potentially the lowest safe dose that remains effective in reducing agitation. In addition, the data collected in Part B will be from a larger number of sites and raters which enables a more accurate estimate of variance for powering future Phase 3 development studies. Some subjects may be asked to participate in the optional sub-study in APPENDIX A. **Efficacy**: Efficacy measurements will be taken up to and including 24 hours post-first dose. The effects of BXCL 501 on acute agitation will be assessed by the following scales: Pittsburgh Agitation Scale (PAS), PEC, the Cohen Mansfield Agitation Inventory (CMAI), CGI-S, and CGI-I. If there is no significant improvement in CGI-I (1 or 2 as "very much" or "much improved", respectively) and there are no evident safety concerns, a second film (of same assignment active vs. placebo) may be given. **Safety**: Adverse events, clinical laboratory tests, 12-lead electrocardiogram (ECG), Johns Hopkins Fall Risk Assessment score, and vital signs will be monitored and recorded. 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 CDC 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.
Number of subjects (planned): At least 30 subjects will be enrolled and randomized at approximately 4 study sites in the United States. [redacted] CCI [redacted]

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CCI [redacted]

Subjects:

Eligible individuals with any form of dementia who have a history of recent agitation (within 6 months or less of enrollment) or their legally authorized representative (LAR) will sign an informed consent form (ICF) before any study-related procedures are performed. Upon confirmation of eligibility, subjects in Cohorts 1, 2, and 3 will be randomized to either BXCL501 or placebo film in a 4:1 randomization. The additional 20 subjects to be enrolled in Cohort 2 will be randomized to either BXCL501 or placebo on a 1:1 randomization. Subjects in Cohort 3 will first enter the 1-week safety observation to assess eligibility, after which they will be screened and randomized to either BXCL501 or placebo. Once subjects become agitated, they will proceed with Day 1 assessments.

The above consent procedures will apply to the additional subjects in Part B who will randomized 1:1 to BXCL501 40 µg or matching placebo film. The criteria for eligibility for patients in Part B remain the same as for those in Cohorts 1 and 2 with the exception of patients who have dementia associated with Parkinson's disease and/or Lewy Body Disease. These patients will be excluded from Part B.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

1. Male and female patients 65 years and older.
2. Patients who have met DSM-5 criteria for neurocognitive disorder or dementia who have history of instances of acute agitation.
3. History of 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.
4. Patients who meet the International Psychogeriatric Association (IPA) diagnostic criterion for agitation.
5. Patients 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.
6. Patients who have a score of ≥2 on at least 1 of the 4 items on the PAS.
7. Patients who read, understand, and provide written informed consent, or who have a LAR.

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8. Patients who are in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology, and urinalysis, and in the opinion of the Principal Investigator.
9. 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 1 week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include the rhythm method, withdrawal, condoms alone, or diaphragm alone.

Exclusion Criteria

1. For Part B: Patients who have dementia associated with Parkinson's disease and/or Lewy Body Disease, if etiology of dementia is known.
2. Patients with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription drugs during urine screening excludes the subject.
3. Patients treated within 4 hours prior to study drug administration with benzodiazepines, other sedatives, hypnotics, or antipsychotics must be excluded.
4. Treatment with alpha-1 noradrenergic blockers or alpha-adrenergic antagonists within 8 hours prior to dosing.
5. No new chronic medications initiated in the past 14 days prior to screening, excluding over-the-counter products taken sporadically.
6. Patients 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).
7. Patients who have hydrocephalus, seizure disorder, or history of significant head trauma, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, or focal neurological findings, with a recent large (non-microvascular) stroke who may be considered medically unstable or in recovery must be excluded. Patients with a remote history of stroke may be included, regardless of size/location.
8. 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 systolic BP or ≥10 mmHg drop in diastolic, or dizziness or lightheadedness), bradycardia, or baseline

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(pre-dose) measurements of heart rate <60 bpm, SBP <110 mmHg, or DBP <70 mmHg must be excluded.

Note: Subjects in Cohort 3 who have OH on more than 1 instance in the same day during the 1-week safety observation period must be excluded.

9. Patients 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.
10. Cohort 3 only: Patients who are taking nitrates or beta blockers shall be excluded. Any other anti-hypertensives should be maintained in the course of the study.
11. Patients 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.
12. Patients who have received an investigational drug within 30 days prior to the current agitation episode must be excluded.
13. Patients who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine or who are unable to use the sublingual film must be excluded, e.g., patients with a history of allergic reactions to dexmedetomidine.
14. Patients experiencing clinically significant pain, per investigator.
15. Cohort 3 only: Patients who are a high fall risk assessed via the Johns Hopkins Fall Risk Assessment (total score >13) or during the 1-week safety observation period will be excluded from further study participation.
16. Pregnancy.

Table 3.1: Schedule of Events

Activity	Pre-Screening[8,9]	Screening	Pre-Dose[1]	Treatment Evaluation Day 1									Day 2 Follow-Up (+1 day)	Day 3	Day 7 (+2 days)
Time point	Pre-treatment	Pre-treatment	-1 hr to time 0	5 min	10 min	15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	24 hr (-9/+12 hr)		End of Study
Informed consent	X														
Medical history	X	X													
Demographics	X	X													
Weight	X												X		
Height	X														
Mini-Mental State exam	X												X		
Clinical Dementia Rating Score	X												X		
Physical exam	X	X											X		
Safety laboratory assessments[3]	X													X	X
UDS[10]	X	X[11]													
UTI and pregnancy		X													
Johns Hopkins Fall Risk Assessment (Cohort 3 only)	X														
ECG with rhythm strip[7]	X		X						X				X		
Pulse oximetry			X				X	X	X	X	X	X	X		
Resting vital signs[2]	X	X	X				X	X	X	X	X	X	X		
Orthostatic vital signs[2]	X	X	X				X	X	X	X		X	X		

Activity	Pre-Screening[8,9]	Screening	Pre-Dose[1]	Treatment Evaluation Day 1									Day 2 Follow-Up (+1 day)	Day 3	Day 7 (+2 days)
Time point	Pre-treatment	Pre-treatment	-1 hr to time 0	5 min	10 min	15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	24 hr (-9/+12 hr)		End of Study
Inclusion/Exclusion criteria	X	X	X												
Randomization			X												
CMAI		X	X						X						X
Study drug administration[6]			X												
PAS	X	X	X				X	X	X	X		X	X	X	X
PEC[12]	X		X				X	X	X	X		X	X	X	X
ACES			X					X	X	X		X			
CGI-Severity (agitation)			X						X				X		
CGI-Improvement (change in agitation)							X	X	X	X		X			
C-SSRS	X	X											X		
Buccal (SL) assessment[5]				X	X	X	X		X	X			X		
PK sampling[4]							X	X	X*	X		X	X		
Concomitant medications	X	X	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	X	X	X	X

CCI [redacted]


CCI

Table 3.2: Schedule of Events – 1-week Safety Observation (Cohort 3 Only)

Activity	Day O1		Day O2		Day O3		Day O4		Day O5		Day O6		Day O7	
Time point	**AM**	**PM[1]**	**AM**	**PM[1]**	**AM**	**PM[1]**	**AM**	**PM[1]**	**AM**	**PM[1]**	**AM**	**PM[1]**	**AM**	**PM[1]**
Resting vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of falling and syncope	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	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	X	X	X
CCI	[redacted]													

4. TABLE OF CONTENTS

4.1. LIST OF TABLES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse event
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AUC	Area under the plasma concentration vs time curve
BP	Blood pressure
BMI	Body mass index
C	Celsius/Centigrade
CDR	Clinical Dementia Rating Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CLIA	Clinical Laboratory Improvement Amendments
CMAI	Cohen-Mansfield Agitation Inventory
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ET	Early termination
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic Act
g	Gram
GABA	Gamma-amino butyric acid
GCP	Good Clinical Practices
HCl	Hydrochloride

Abbreviation	Definition
HR	Heart rate
hr	Hour
ICH	International Council for Harmonisation
ICU	Intensive care unit
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram
LAR	Legally authorized representative
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LD	Listed drug
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minutes
mL	Milliliter
mm	Millimeter
mmHG	Millimeters of mercury
MMRM	Mixed model repeated measures
MMSE	Mini Mental Status Exam
MS	Mass spectrometry
MTD	Maximum tolerated dose
MW	Molecular weight
PANSS-EC/PEC	Positive and Negative Syndrome Scale/ Positive and Negative Syndrome Scale – Excited Component
PAS	Pittsburgh Agitation Scale
PD	Pharmacodynamics
pg	Picogram
pH	Measure of hydrogen ion concentration
PI	Principal Investigator
PK	Pharmacokinetic

Abbreviation	Definition
po	Oral/By mouth
POC	Proof of Concept
PP	Per Protocol
RASS	Ramsay Sedation Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SL	Sublingual
THC	Tetrahydrocannabinol
T_{max}	Time that drug is present at the maximum concentration in serum
µg/µcg	Microgram
UDS	Urine drug screen
US	United States
USP	United States Pharmacopeia

6. INTRODUCTION

6.1. Background and Rationale

Background

Agitation is a severe, disruptive, and morbid complication of many chronic mental illnesses, including schizophrenia (Osser and Sigadel, 2001), dementia (Conn and Lieff, 2001), and bipolar disorder (Alderfer and Allen, 2003). Currently, the standard of care in the treatment of acute agitation in the demented elderly population is anti-psychotics and or benzodiazepines. Though efficacy has been demonstrated for each of these agents, older people are more sensitive to the side effects produced by these drugs and in fact there are issues with mortality associated with the use of anti-psychotic drugs in this population (Salzman et al., 2008). In addition, onset of action after both oral and intramuscular administration of some of these agents is typically 30-60 min due to slow absorption into the systemic circulation. Slow onset of action can extend the suffering of agitated patients and increases the need for physical restraint or seclusion (Allen et al., 2003). According to expert consensus guidelines developed by 50 leading US experts in behavioral emergencies (Allen et al., 2001), speed of onset of anti-agitation effects was viewed as one of the most important factors in selecting an agitation treatment. An alternative non-invasive, potentially safer medication which produces a rapid calming effect that allows patients to participate in their care and treatment would find use in the pharmacological management of acute agitation.

BioXcel Therapeutics, Inc. is developing a sublingual film formulation of dexmedetomidine (BXCL501) for the acute treatment of hyper-arousal in agitated patients with schizophrenia, bipolar disorder, and dementia. Dexmedetomidine is a highly selective α2 adrenoceptor agonist on presynaptic neurons. The stimulation of these receptors in the locus coeruleus leads to a decrease in norepinephrine release from presynaptic neurons with inhibition of postsynaptic activation, which attenuates central nervous system (CNS) arousal, and diminishes the fight-or-flight response (MHRA, 2014). [redacted] In addition, because it enters the blood stream directly by the sublingual route and bypasses first-pass metabolism in liver, dexmedetomidine from BXCL501 is less susceptible to variations in hepatic function than orally administered drugs.

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

Dexmedetomidine has been administered by the oral, nasal, and oral mucosal routes in both nonclinical and clinical studies as reported in the published literature, with no route-specific safety signals (oral mucosal or gastrointestinal) identified. In healthy volunteers and patients with agitation associated with schizophrenia (Studies BXCL501-101 and BXCL501-102, respectively) single doses of 10 µg to 180 µg BXCL501 produced systemic dexmedetomidine exposures (C_{max} and AUCs) substantially lower than Precedex use for procedural anesthesia with no local tolerability issues.

This study will test a range of doses which are projected to expose subjects to plasma levels of dexmedetomidine that were associated with a safe and effective anti-agitation effect as measured by a reduction in PEC scores using the reference IV product. From the reference product, we know the most significant AEs are bradycardia/hypotension and unarousable sedation stemming from a more rapid delivery of greater doses and higher exposures which produce anesthesia. The range of doses selected should remain well below exposure associated with IV induction of anesthesia, although somnolence may be observed with higher doses of BXCL501. In addition, the stopping criterion are focused on cardiovascular AEs and excessive sedation. Agitated subjects are frequently dehydrated and exhausted from psychomotor activity. Thus, while elevated vital signs typically accompany agitation, as a calming effect is achieved, if unaccompanied by rehydration and rest, there may be a greater propensity for sensitive subjects to experience cardiovascular AEs or appear excessively somnolent especially in this population. With respect to sedation, recovery from prolonged excessive psychomotor activity naturally includes restfulness and eventual sleep. Differentiating natural sleep because of successful calming treatment as opposed to that associated with drug exposure is therefore problematic. Particularly with higher doses we expect to encounter mild to moderate somnolence, sleepiness or drowsiness and will monitor for excessive sedation using the ACES assessment. The ability to arouse a subject differentiates ACES score of 8 (deep sleep) from 9 (unarousable sleep), a level which we will assume is an unacceptable effect representing excessive sedation.

This study is designed to accomplish adaptive rapid dose-ranging based on POC data on clinical effectiveness and what is known of extensive safety and tolerability of higher doses delivered rapidly via IV. A site-based escalation schema with focused periodic safety review allows testing multiple dose cohorts with the lowest doses tested first, and higher doses last. Although each individual site accrues experience with a small number of serially assigned escalating doses, at an overall study level, higher dose panels accrue slowly enough to identify early safety/tolerability signals in small numbers long before high dose panels complete enrollment. An additional element allows investigators to repeat a dose for lack of efficacy, which provides rich data on proportion of responders/non-responders while effectively augmenting testing safety of exposure to the next greater dose level.

6.2. Description of BXCL501

[redacted]
CCI
[redacted]

No special transport or storage conditions are required for BXCL501. Packaged films can be stored at room temperature (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 (MHRA, 2014).

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

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

6.4. Clinical Experience and Pharmacokinetics

6.4.1. Single Ascending Dose Study (Study BXCL501-101)

This study was a single site, randomized, double-blind, placebo controlled, PK, safety, and tolerability study with 4 dosing, groups. Healthy adults 18–65 years of age, both males and females, were included in this study.

The primary objective of this study was to determine the PK, safety, and tolerability of the various film strengths of BXCL501 for identification of appropriate film dosage strengths to be carried forward into subsequent clinical trials.

The study evaluated 3 doses of BXCL501 film in 4 cohorts of healthy adult male and female participants. In Cohorts 1 and 2 (10 µg and 20 µg), 12 new participants were enrolled per cohort, randomized in a ratio of 2:1, with 8 patients receiving BXCL501 film and 4 patients receiving placebo film. Cohort 3 and 4 (40 µg) included participants receiving active treatment who had completed treatment in Cohorts 1 or 2, as well as new participants. Single doses up to 40 µg BXCL501 were well-tolerated. Following a blinded safety review of Cohort 3, the study accrued additional subjects at 40 µg and did not escalate to 60 µg, per protocol in Cohort 4. [redacted]

The PK population evaluated 3 dose levels: 10, 20, and 40 µg. The 10 µg and 20 µg dose levels consisted of 8 subjects, while 40 µg dose level consisted of 12 subjects treated with dexmedetomidine. Each dose level consisted of active and placebo subjects in a 2:1 ratio.

[redacted]

[redacted]

6.4.2. CCI [redacted]

CCI [redacted]

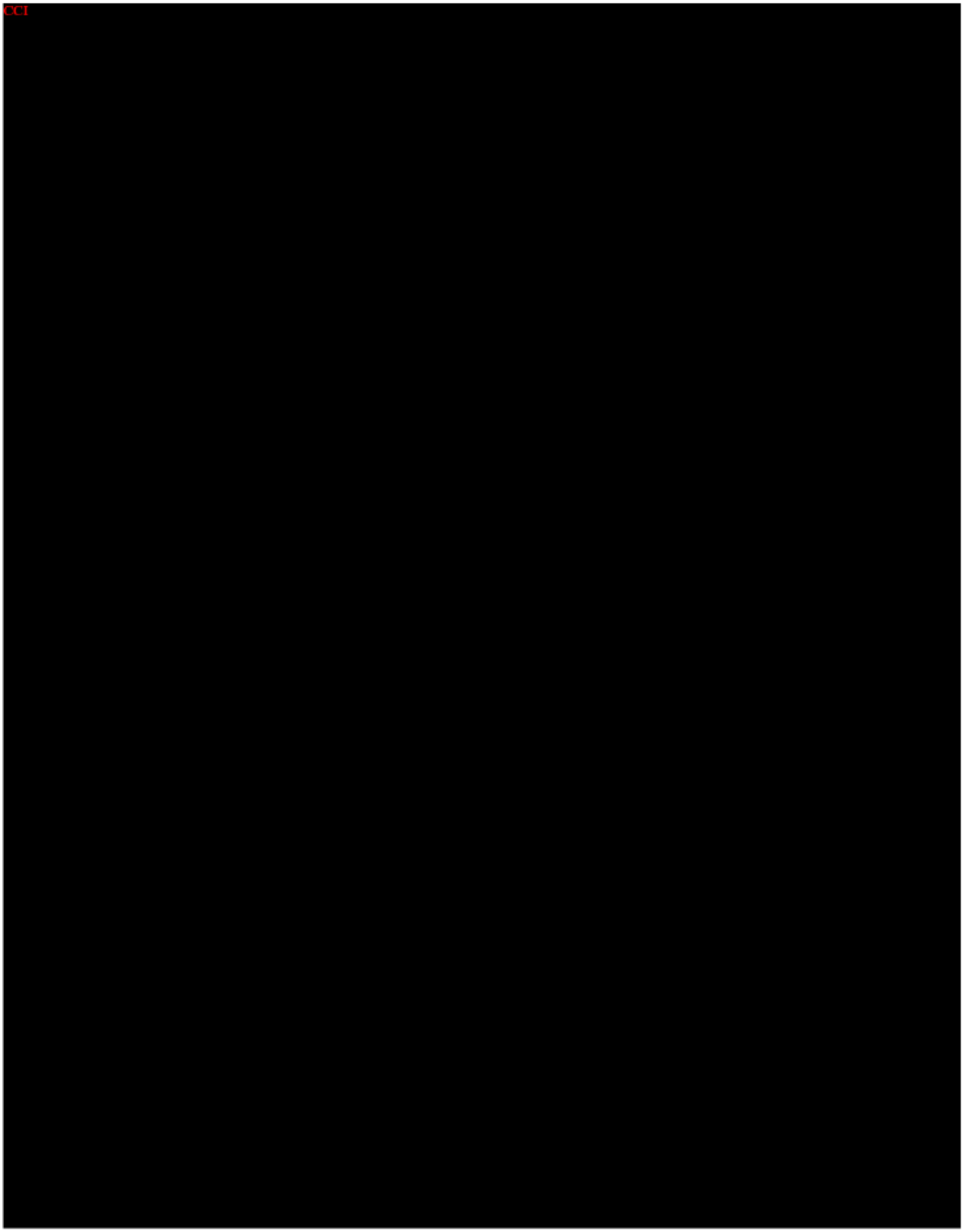
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Table 6.1: Preliminary Study Output from Study BXCL501-102

Dose (ug)	N	C_{max} (ng/L)	AUC_{last} (ng•h/L)	AUC_{inf} (ng•h/L / L)	T_{max} (hr)	$T_{½}$ (hr)
20	10	37 (44%)	160 (45%)	239 (28%)	1.7 (1 -4)	3.2 (31%)
60	18	133 (34%)	577 (60%)	675 (61%)	1.5 (1 – 4)	2.6 (40%)
80	18	155 (42%)	817 (60%)	983 (55%)	1.6 (1.2 – 4.3)	3.2 (36%)
120	18	221 (43%)	1170 (79%)	1378 (72%)	2.0 (1 – 4)	3.3 (43%)
180	18	379 (68%)	2294 (88%)	2760 (91%)	2.0 (1 – 8)	3.2 (53%)

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7. OBJECTIVES

7.1. Primary Endpoint

The primary objective of this trial is to:

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

7.2. Secondary Endpoints

The secondary objectives of this trial are to determine:

1. Describe the onset and magnitude of calming effects of different doses of BXCL501 on symptoms of acute agitation associated with dementia as measured by the Pittsburgh Agitation Scale (PAS) and PANSS-EC (PEC) as compared to placebo.
2. Describe the duration of calming as measured by PEC and ACES.
3. Describe the tolerability and safety profile of BXCL501, as determined by adverse events and vital signs vs. placebo.
4. Describe clinical effects as measured by Clinician Global Impression of Severity (CGI-S) scale for agitation and then improvement (CGI-I) after drug administration.
5. Describe the frequency of agitated behaviors using the CMAI at baseliner and 2 hours post-dose.
6. Determine the approximate dissolution time of BXCL501 films in the sublingual space.
7. Assess the local tolerability via buccal examination after dosing BXCL501 film.
8. Describe the PK and exposure of dexmedetomidine as delivered by sublingual BXCL501 dosing.
9. Part B: Describe the duration of calming as measured by the 3 supplementary items of the PANSS.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is an adaptive Phase Ib/II trial design. It is 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.

The study will attempt to characterize a safe and tolerable dose range that results 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 levels. It is possible that the sponsor will opt to expand the number of sites and subjects per dose arm as the study progresses. This adaptive design is beneficial as it yields more extensive safety and tolerability data, increases confidence in efficacy by capturing variability in response and exposure, while providing data that is more generalizable for later phase trials. As such, an additional 20 patients will be enrolled into the 60 µg Cohort. These additional subjects will provide significantly more safety data at the 60 µg dose, but also a greater imbalance with respect to placebo (pooled across cohorts) under the original 4:1 randomization ratio (BXCL501:placebo). Accordingly, to facilitate more informative comparisons to placebo, the additional 20 subjects will be randomized at a 1:1 ratio of BXCL501:placebo. This achieves the overall randomization ratio as originally designed.

Forty-six patients in Part B of this study will be randomized in a 1:1 ratio to receive BXCL501 40 µg or matching placebo film.

Eligible patients (those with any type of dementia) may be identified in skilled nursing facilities, mental health, psychiatric or medical emergency services including medical/psychiatric observation units, or as newly admitted to a hospital setting for acute agitation or already in hospital for chronic underlying conditions. Subjects will remain in their facility while undergoing screening procedures to assess eligibility.

Patients in Part B of this study will be seniors age 65 and above, who are semi-independent, and able to carry out many of their activities of daily living under minimal supervision, such as those who reside in assisted living facilities.

The study will consist of a pre-screening/screening period, treatment period, and a follow-up period. Evaluation of 3 doses of 30 µg, 60 µg, and 90 µg (Cohort 1, Cohort 2, and Cohort 3, respectively) are planned, with an option to test different doses based on tolerability and safety.

Pre-Screening and Screening Period

Cohort 1 and Cohort 2

During the screening period, patients assigned to Cohort 1 or Cohort 2 will be assessed for their eligibility by undergoing Pre-Screening and Screening visit assessments as outlined in the Schedule of Events (Table 3.1). The Pre-Screening visit may occur no more than 28 days before first dose of study treatment.

Cohort 3

The Pre-Screening visit assessments, as outlined in Table 3.1, must be started within 28 days before the first dose of study treatment. After completion of the Pre-Screening assessments and review of labs and ECGs, subjects assigned to Cohort 3, if eligible, will participate in a 1-week safety observation. During this 1-week safety observation period, subjects will receive in-patient safety assessments as outlined in Table 3.2 to evaluate their risk for falling and syncope with twice daily BP and orthostatic BP measurements, and recording of instances of falling and syncope.

At the Pre-Screening visit, if a subject is a High Fall Risk (>13) via the Johns Hopkins Fall Risk assessment, they will be excluded from study participation and re-screen will not be permitted. If a subject has OH on more than 1 instance in the same day during the 1-week safety observation period, they will be excluded from study participation. Following the 1-week safety observation period, subjects will complete the Screening visit as outlined in Table 3.1.

Patients in Part B of this study will follow the same schedule of events as outlined in the Schedule of Events (Table 3.1). The Pre-Screening visit may occur no more than 28 days before first dose of study treatment.

Treatment Period

Upon confirmation of eligibility, subjects will be randomized within their dose cohort to receive a single 30 µg, 60 µg, or 90 µg dose, respectively, of BXCL501 or placebo film.

For Part B of this study, subjects will be randomized to receive a single dose of BXCL501 40 µg of or matching placebo film.

Up to 1 hour prior to dosing, pre-dose vital signs, including BP, orthostatic BP, will be collected. If OH is observed or if SBP <110 mmHg, then the subject will be hydrated and dosing will be delayed until OH is resolved. Every effort will be made to keep the subject sitting or lying down for at least 2 hours after dosing.

After pre-dose vitals have been collected, a single dose of BXCL501 or placebo film will be administered sublingually by the patient if able with instructions from an unblinded staff member who will not participate in evaluation of safety or efficacy. The drug film will be retained in the sublingual cavity until dissolved. Participants will also be evaluated for local irritation around the area where the film is placed. Efficacy and safety assessments will be conducted periodically before and after dosing. The next cohort will be dosed after completing accrual of most prior panels, in accord with regular ongoing periodic safety and PK review as eligible subjects are assigned, dosed, and data becomes available.

Vital signs and ECGs will be conducted at the time points indicated in the schedule of events. Participants will be allowed water as desired 15 minutes after completion of dosing. Safety and tolerability assessments will be continued until the morning of Day 3 and will be repeated on Day 7 + 2 days. Smoking will be permitted according to the site's policies. After the 4 hour assessments are completed, at the discretion of the PI, rescue therapy may be initiated using standard of care treatment which may include lorazepam 0.5-5 mg po/IM or an antipsychotic medication po/IM.

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 of no clinical significance. Subjects presenting with a clinically significant urinary tract infection (UTI) as determined by clinical laboratory tests will be excluded from the study.

A nurse will be present prior to dosing and remain present for at least 6 hours after dosing or longer if needed, until any safety concerns, intolerability or adverse events resolve. If dose-limiting safety or intolerability is determined, further dosing of a cohort may be stopped, and escalation discontinued.

The PK plasma samples should be collected per the Schedule of Events (Table 3.1).

This is an adaptive design as doses selected for testing may be different from these, based upon safety reviews. Doses lower or higher may be chosen to test, and repeated, up to 180 µg within each cohort, and additional subjects may be added to a cohort. BXCL501 films may be divided in half if needed to deliver half-dose strengths. Except for Cohort 1, each subsequent dose level will be authorized after a safety review of the previous dosing cohort. Dosing may be repeated in the case of persistent or recurrent agitation, if there is no significant improvement (CGI-I of 1 or 2 as "very much" or "much improved") and no safety events evident. Dosing may be repeated up to a total of two repeat doses (at the same randomization group BXCL501:placebo) for all cohorts except for 90 µg dose which can only be repeated once (total 180 µg) if necessary, at 2 hours post first dose but only after the 2 hour assessments are conducted and only within 12 hours post first dose. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than 90/60 diastolic/systolic) and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of 20 points in either SBP or DBP) or if they are experiencing an AE. Not only does this determine individual response to a single dose, but it also determines if a given subject is responsive to a second dose and may respond to a greater dose, or could be categorized as a non-responder to BXCL501 despite being exposed to a greater total dose.

Some subjects may be asked to participate in the optional sub-study in APPENDIX A.

Periodic safety data reviews will be undertaken on an ongoing basis to review all subjects assigned and dosed, as data and analyses become available. Dose escalation will be allowed unless a safety or tolerability issue becomes evident upon periodic regular safety review.

Patients enrolling at a site are sequentially assigned to the lowest dose cohort (including placebo) followed by enrollment assignment to increasing dose cohorts. This sequential escalating adaptive enrollment ensures subject safety; the lowest dose cohort completes accrual first, higher dose cohorts complete last. In addition, those subjects assessed as requiring a second dose for efficacy provide early evidence of safety/tolerability of higher doses as they are effectively exposed to doses that approximate the next dose cohort. The majority of patients will be enrolled and evaluated in lower dose cohorts before a higher dose cohort is initiated. Further, if evidence of intolerability arises from analyses integrating PK, exposure and safety/tolerability of all subjects and doses, the dose regimen may be altered, or a different dose may be selected to test the hypothesis that a (typically lower) dose regimen is better tolerated.

In addition to periodic ongoing safety reviews, after accruing each dose cohort a safety and tolerability review will be done by the BioXcel Therapeutics, Inc. medical monitor, clinical pharmacologist, and the PI's (blinded), who will decide to continue or may stop the study. If dose-limiting safety or intolerability is determined, further dosing of a cohort may be stopped, and escalation discontinued.

Further assignment to the same dose will be halted, and escalation will be discontinued for the following drug-related adverse events (dose-limiting toxicity, DLT) classified by CTCAE version 5.0;

- One Grade 3 or greater cardiovascular event (e.g., symptomatic sinus bradycardia that requires invasive intervention)
- Three Grade 2 cardiovascular events (e.g., a significant cardiovascular event which was both symptomatic and required treatment with an active pharmacologic intervention (required IM/IV medication administration in addition to standard supportive care/ observation/monitoring/hydration).
- Three Grade 3 or greater sedation events (depressed level of consciousness where subject is difficult to arouse, or somnolence to the point of obtundation or stupor). For DLT events reported in subjects who received a second dose, sponsor may elect to alter the dose regimen (e.g., repeated dosing may be discontinued or allowed only after an elapsed time) and continue to accrue subjects or initiate a different dose to test the hypothesis that a lower dose remains safe and well tolerated.

AEs of moderate somnolence, excessive sleepiness and drowsiness will be considered acceptable for the condition as these may be considered part of the natural course of recovery from agitation and/or a consequence of an adequate treatment intervention.

Dose selection criterion are dependent upon the emergent safety and tolerability as well as clinical effectiveness. Because these each remain to be tested, criteria for dose selection may be adapted as data is acquired (e.g., evidence of robust efficacy at the lowest tested dose could shift low dose criterion to a higher proportion for efficacy).

Follow-up Period

The Follow-up Period will encompass the Day 2 Follow-Up and the Day 3 visits as detailed in Table 3.1.

Subjects will also be required to undergo a Day 7 End of Study visit, in which the CMAI, PEC, and PAS, along with safety assessments, will be performed.

8.2. Stopping Criterion

The following stopping criterion will be employed: if a given cohort has 2 drug-treated patients experiencing syncope or a single syncope related fall, dosing will be suspended. After a thorough unblinded safety review, the cohort may be stopped, and testing may continue at the same or lower dose selected based on the safety review assessment.

In Part B of the study, given that the 60 µg dose was safe and well tolerated, the stopping criteria is deemed unnecessary for the 40 µg dose.

8.3. Study Sites

The study will take place at approximately 4 centers in the US.

9. SUBJECT POPULATION

9.1. Selection of Study Population

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 patients 65 years and older.
2. Patients who have met DSM-5 criteria for neurocognitive disorder or dementia who have history of instances of acute agitation.
3. History of 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.
4. Patients who meet IPA diagnostic criterion for agitation.
5. Patients 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.
6. Patients who have a Score of ≥2 on at least 1 of the 4 items on the PAS.
7. Patients who read, understand, and provide written informed consent, or who have a LAR.
8. Patients who are in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology, and urinalysis, and in the opinion of the Principal Investigator.
9. 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 1 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, IUD, condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include: the rhythm method, withdrawal, condoms alone, or diaphragm alone.

9.1.2. Exclusion Criteria

1. For Part B: Patients who have dementia associated with Parkinson's disease and/or Lewy Body Disease, if etiology of dementia is known.
2. Patients with agitation caused by acute intoxication must be excluded. Positive identification of non-prescription drugs during urine screening excludes the subject.
3. Patients treated within 4 hours prior to study drug administration with benzodiazepines, other sedatives, hypnotics, or antipsychotics must be excluded.

4. Treatment with alpha-1 noradrenergic blockers, alpha adrenergic antagonists within 8 hours prior to dosing.
5. No new chronic medications initiated in the past 14 days prior to screening excluding over-the-counter products taken sporadically.
6. Patients 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 C-SSRS.
7. Patients who have hydrocephalus, seizure disorder, or history of significant head trauma, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, or focal neurological findings, with a recent large (non-microvascular) stroke who may be considered medically unstable or in recovery must be excluded. Patients with a remote history of stroke may be included, regardless of size/location.
8. 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 systolic BP 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.

   Note: Subjects in Cohort 3 who have OH on more than 1 instance in the same day during the 1-week observation period must be excluded.
9. Patients 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.
10. Cohort 3 only: Patients who are taking nitrates or beta blockers shall be excluded. Any other anti-hypertensives should be maintained in the course of the study.
11. Patients 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.
12. Patients who have received an investigational drug within 30 days prior to the current agitation episode must be excluded.
13. Patients who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine, or unable to use the sublingual film, must be excluded, e.g., patients with a history of allergic reactions to dexmedetomidine.
14. Patients experiencing clinically significant pain, per investigator.
15. Cohort 3 only: Patients who are a high fall risk assessed via the Johns Hopkins Fall Risk Assessment (total score >13) or during the 1-week safety observation period will be excluded from further study participation.
16. Pregnancy.

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.

In each of the 3 dose cohorts, patients will be randomized in a 4:1 ratio of BXCL501:placebo. However, after beginning enrollment in the 90 µg Cohort , a decision was made not to continue to enroll , but rather to enroll an additional 20 subjects in the 60 µg . This will result in significantly more safety data at that dose, but also a greater imbalance with respect to placebo (pooled across cohorts) under the original 4:1 randomization ratio (BXCL501:placebo). Accordingly, to facilitate more informative comparisons to placebo, the additional 20 subjects will be randomized at a 1:1 ratio of BXCL501:placebo. This achieves the overall randomization ratio as originally designed.

In Part B, the inclusion of an additional 46 subjects will assess the efficacy and safety of a 40 µg dose of BXCL501 or placebo in a 1:1 randomization ratio.

Study randomization will be computer generated.

10.2. Identification of Investigational Product

BXCL501 will be provided as a small, solid-dose film formulation, approximately 22 mm × 13 mm, and less than 1 mm thick, designed to immediately adhere to the SL mucosa and to solubilize in 1-2 minutes.

BXCL501 Sublingual Film 60 µg, and placebo are packaged as individual films in heat-sealed white foil pouches with a label. The pouch has a white colored outer layer with foil colored inner layer. Individual film appearance is as follows:

- 60 µg – green rectangular thin film (~22 mm × 12.8 mm) with 2 blue spots
- Placebo – green rectangular thin film (~22 mm × 12.8 mm) with or without 2 blue spots

In addition to these films, 120 µg green rectangular thin films (~22 mm × 12.8 mm) with 2 darker colored spots and 180 µg green rectangular thin films (~22 mm × 12.8 mm) with 2 darker colored spots may be provided to the sites and administered as appropriate.

For Part B of the study, BXCL501 Sublingual Film 80 µg, and placebo are packaged as individual films in heat-sealed white foil pouches with a label. The pouch has a white colored outer layer with foil colored inner layer. Individual film appearance is as follows:

- 80 µg – green rectangular thin film (~22 mm × 12.8 mm) with 2 blue spots
- Placebo – green rectangular thin film (~22 mm × 12.8 mm) with or without 2 blue spots

BioXcel Therapeutics, Inc. will provide an adequate supply of study drug to the sites.

10.3. Treatment Administration

Dosing may be achieved by cutting of a film, widthwise, directly in the middle, to make a half dose. Dosing may also be achieved by administration of 1 to 2 films (e.g., a 120 µg dose may be

cut in half and administered to make a 60 µg dose or a 180 µg dose may be cut in half and administered to make a 90 µg dose). At the beginning of each study session, patients will be instructed on how to self-administer the investigational product. If the patient can self-administer, he/she will self-administer the dose of BXCL501 or placebo film sublingually under supervision of an unblinded staff member who will not participate in evaluation of safety or efficacy. The investigational product will be retained in the sublingual cavity until dissolved. If sublingual administration is not possible, the film may be placed inside the lower lip. The location of the placement of the film should be noted in the subject's chart. Objective buccal mucosal examination and time of film dissolution by unblinded study staff per Table 3.1 will be conducted.

In Part B, dosing will be achieved by cutting of an 80 µg film, widthwise, directly in the middle, to make a 40 µg dose.

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 FDA 1572, designated staff, and subjects in this study. The investigator will not dispense study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

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

10.7. Blinding and Unblinding Treatment Assignment

This study will be conducted under double-blind conditions so that neither the subject nor the Investigator or study staff members will know the identity of each subject's treatment. BXCL501 or placebo film will be provided and administered per Section 10.3 of this protocol.

Treatment assignment for an individual subject should be unblinded only in an emergency, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The Investigator should contact the medical monitor 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 6.2, 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. In Study BXCL501-102 patients with agitation associated with schizophrenia, single doses up to 180 ug were administered with no serious adverse effects. The highest proposed total daily dose in the current study is also 180 ug, but the starting dose is only 30 ug, which provides an adequate safety margin if the PK, safety and/or tolerability is substantially different in the dementia population compared to the schizophrenic population.

Analysis of the 30 and 60 µg cohorts revealed both doses were well tolerated with the 60 µg dose demonstrating efficacy vs. placebo on each independent measure of agitation. Although not reaching statistical significance, the 30 µg dose changes paralleled the statistically significant reductions in agitation observed for the 60 µg dose group, with a numerical improvement versus placebo on the PEC and PAS ratings over 8 hours. As such, the sponsor decided to explore efficacy and safety of a 40 µg dose cohort as an intermediate dose between 30 µg and 60 µg. The objective of Part B is to test a dose of 40 µg as potentially the lowest safe dose that remains effective vs. placebo in reducing agitation. In addition, the data collected in Part B will be from a larger number of sites and raters which enables a more accurate estimate of variance for powering future Phase 3 development studies.

10.9. Treatment Compliance

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

10.10. Concomitant Medications

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

10.10.1. Permitted Therapies

Concomitant medications are allowed (unless specifically prohibited) 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 PI, 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 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 study treatment and the indication (insomnia) must be clearly recorded in CRF and source documents.

10.10.2. Prohibited Therapies

The following medications are prohibited within 4 hours prior to BXCL501 dosing:

> Sedative/hypnotics, barbiturates, anxiolytics (including benzodiazepines), antihistamines (e.g., diphenhydramine), sedating antidepressants (mirtazapine, trazodone), triptans (e.g., sumatriptan), opioids.

The following medications are prohibited from 4 hours prior, until 6 hours post-dose, unless clinically indicated:

> Antiarrhythmics, antibiotics/antifungals/antivirals, anticholinergics, anticonvulsants, antihypertensive (specifically other alpha-adrenergic medications including clonidine, guanfacine, prazosin), anxiolytics or sedative-hypnotics, centrally acting calcium antagonist, cholinomimetics, migraine-serotonin receptor agonist, opioids.

Antihypertensives or other medications can be held on the day of the dosing at the discretion of the investigator.

11. STUDY PROCEDURES

Subjects or their LAR will provide written informed consent, and assent as applicable, before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

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

Cohort 3 subjects, who will participate in the 1-week safety observation period, will also follow the assessments provided in Table 3.2.

For Part B, the 3 PANSS Supplementary Items will be done at the times the PEC is conducted, including the different timepoints throughout the study, listed below from Section 11.1 to Section 11.7.

11.1. Pre-Screening

Subjects must be pre-screened, screened, and randomized into the study before dosing. When possible, screening and randomization will take place on the same day.

The following procedures will be performed at Pre-Screening (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
- Resting and orthostatic vital signs
- Record medical history, including prior and current therapies (e.g., prescription and non-prescription medications)
- Physical examination including weight, height, and body mass index
- 12-lead ECG with rhythm strip
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and UDS)
- MMSE
- CDR score
- PAS
- PEC
- C-SSRS
- Cohort 3 only: Johns Hopkins Fall Risk Assessment Tool
- Assess and record AEs

11.1.1. One-week Safety Lead-in (Cohort 3 Only)

After completion of the Pre-Screening assessments and review of labs and ECGs, subjects enrolled into Cohort 3, if eligible, will participate in a 1-week safety observation period. During this 1-week observation period, subjects will be assessed twice daily for their BP and orthostatic BP measurements, along with recording of instances of falling and syncope, and assessment of AEs and concomitant medications. After the conclusion of the 1-week observation period, subjects in Cohort 3 will complete the screening visit and follow all subsequent visit schedules as outlined in Table 3.1.

11.2. Screening

- Record medical history, including prior and current therapies (e.g., prescription and non-prescription medications)
- Collect demographic information
- Physical examination
- UTI and pregnancy urine screening
- UDS (required for Cohort 3 only)
- Note: UDS will be re-collected for Cohorts 1 and 2 if more than 21 days have passed since the Pre-Screening visit
- Resting and orthostatic vital signs
- Review inclusion and exclusion criteria
- CMAI
- PAS
- C-SSRS
- Record concomitant medication use
- Assess and record AEs

11.3. Pre-Dose

- Review inclusion and exclusion criteria
- Resting and orthostatic vital signs
- Pulse oximetry
- 12-lead ECG with rhythm strip
- Randomization
- Study drug administration
- CMAI
- PAS

- PEC
- ACES
- CGI-S
- Record concomitant medication use
- Assess and record AEs

The Screening Visit may be conducted over more than one day; however, all procedures must be completed prior to subject randomization and within 28 days of signing informed consent.

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

11.4. Day 1, Treatment Evaluation

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):

- Resting and orthostatic vital signs
- 12-lead ECG with rhythm strip
- Pulse oximetry
- CMAI
- PAS
- PEC
- ACES
- Record concomitant medication use
- Assess and record AEs
- 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
- CGI-S
- Buccal (SL) assessment
- PK sampling

11.5. Day 2 (+1), Follow-Up

The following procedures will be performed on Day 2:

- 12-lead ECG with rhythm strip

- Physical exam (including weight)
- Resting and orthostatic vital signs and weight measurements
- Pulse oximetry
- MMSE
- CDR score
- PEC
- PAS
- CGI-S
- Plasma sample for PK analysis at 24 hours ± 1 hour post-dosing
- C-SSRS
- Buccal (SL) assessment
- Record concomitant medication use
- Assess and record AEs

11.6. Day 3

The following procedures will be performed on Day 3:

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- PAS
- PEC
- Record concomitant medication use
- Assess and record AEs

11.7. Day 7 + 2 Days

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

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- CMAI
- PAS
- PEC
- 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 to 35.

12.1.2. Cohen Mansfield Agitation Inventory (CMAI)

Assessment of drug effect on frequency of acute agitation will be also done using the CMAI. The CMAI is a rating questionnaire consisting of 29 behaviors each rated on a 7-point scale of frequency. It is possible that all 29 behaviors will not be relevant to a specific patient. Only behaviors manifest by the subject at baseline will be assessed throughout the study resulting in a modified CMAI. Behaviors which are present immediately pre-dose will be rated throughout the post-dose timepoints. At each timepoint after Pre-dose the rater will note that items (behaviors) which were not manifest prior to dosing have not emerged since last CMAI assessment. Should they emerge, these items shall be included in ratings.

12.1.3. Agitation-Calmness Evaluation Scale (ACES)

The ACES is a single item measure rating overall agitation and sedation, where 1 indicates marked agitation; 2 – moderate agitation; 3 – mild agitation; 4 – normal behavior; 5 – mild calmness; 6 – moderate calmness; 7 – marked calmness; 8 – deep sleep; and 9 – unarousable.

12.1.4. 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, Resting Care.

12.1.5. 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 = Minimally symptomatic- few or mild symptoms -little interference with patients functioning

3 = Mildly symptomatic-low level of symptoms-little interference in social functioning

4 = Moderately symptomatic-some prominent symptoms-some interference in functioning

5 = Markedly symptomatic-significant symptoms with very substantial interference in functioning

6 = Severely symptomatic- very marked symptoms make it difficult for patients to engage with others

7 = Among the most extremely symptomatic subjects-extreme symptoms -patient is incapacitated or highly dangerous to self or others requires extra care and supervision

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 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 points total on this test is 30. Any score of 24 or more (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.

12.2.2. CDR Score

The CDR® (Alzheimer's Disease Research Center, Washington University, St Louis) is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer Disease and related dementias: memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care. A score of 0 connotes no cognitive impairment, and then the remaining four points are for various stages of dementia where:

- CDR-0 = normal
- CDR-0.5 = very mild dementia
- CDR-1 = mild
- CDR-2 = moderate
- CDR-3 = severe.

12.3. Pharmacokinetics

Blood samples (4 mL) will be collected at 0.5, 1, 2, 4, 8 and 24 hours post-dose, and for Part B subjects, an additional sample will be collected if possible, between 10 and 12 hours per the Schedule of Events Table 3.1. The 8 hour sample could have a window of 7-9 hours post dose and the next sample could have a window of 10-12 hours post dose.

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.

For each subject, up to 6 blood samples (24 mL of blood) will be collected during the study for PK analysis. In addition, approximately 15 mL of blood will be collected at screening, approximately 15 mL of blood will be collected at Day 3, and approximately 15 mL of blood will be collected at Day 7 (+2 days) for clinical laboratory testing. The total volume of blood collected during the study is expected to be approximately 69 mL.

For re-dosed subjects only: an extra PK blood sample (4 mL) will be collected at 2.5 hours post-first dose in addition to the other times, totaling approximately 73 mL. All PK sampling will occur only after all other assessments at that time point are conducted.

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 K_2EDTA.
- 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.

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

Tel: PPD

Cell: PPD

12.4. Analytical Procedures

12.4.1. Bioanalytical Sample Analyses

A validated LC/MS/MS procedure will be used to measure plasma concentrations of dexmedetomidine (BXCL501). Samples from subjects who have at least 1 post-dose sample will be analyzed.

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 will be presented. Representative chromatograms and standard curve graphs will 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 will be included in the final report.

12.4.2. Bioanalytical Methodology

The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the appropriate analyte in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

12.5. Safety

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

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 will be collected from the time of the 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 (MedDRA) will be used to code all AEs.

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

The investigator or designee must report any AE that meets the criteria for an SAE (Section 12.5.1.1) to 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:

BioXcel Therapeutics, Inc. 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 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.

12.5.3. C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) (Oquendo, 2003) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS Baseline/Screening version will be conducted at Pre-Screening. The C-SSRS Since Last Visit version will be conducted at Screening and 24 hours post-dosing.

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.

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, and total protein
Urinalysis:	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test:	Conducted by local labs
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 systolic, diastolic blood pressure and heart rate (measured as pulse) will be measured after the subject has been in a recumbent position for at least 5 minutes at the time points specified in the schedule of events. Measurements should be made at least 1 minute apart using the same arm at each visit.

At indicated timepoints orthostatic measurement of systolic, diastolic blood pressure 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:

- Systolic Blood Pressure <90 mmHg
- Diastolic Blood Pressure <60 mmHg
- Pulse <60 bpm

12.5.6. Electrocardiogram

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

12.5.7. Physical Examination

A standard physical examination will be performed at Pre-Screening, Screening, and 24 hours post-dose. 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 Pre-Screening and weight will be measured again at Day 2.

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. In addition, Part B of this study will be analyzed separately and a separate SAP for Part B of this study will be prepared and finalize prior to database lock of Part B.

13.2. Analysis Populations

The following analysis populations are planned:

- Safety Population: All subjects who receive study drug.
- Intent to treat (ITT) Population: All subjects in the Safety Population who have a PEC Score.
- Per Protocol (PP) Population: All subjects in the ITT Population with no major protocol deviations.

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 (BMI), 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).

The primary efficacy endpoint for this study is the PEC total score with a primary time point of 2 hours, which for Part B will be tested versus placebo using a Mixed Model Repeated Measures approach with alpha controlled at the 0.05 level.

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

Irrespective, nominal significance levels will be reported. Additional details will be provided in the Part B SAP.

13.3.3. Safety Analyses

All safety analyses will be performed using the Safety Population. All subjects who received at least 1 dose of study drug will be included in the population for safety analysis.

Adverse events will be characterized by type, severity, seriousness, and relationship to treatment. Adverse events will be coded by preferred term and system organ class using the latest version of MedDRA. Incidence of AEs will be summarized by treatment overall, by severity, and by relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented.

Vital signs, ECG with rhythm strip, and clinical laboratory results will be summarized by treatment. Physical examination findings will be listed.

13.3.4. Pharmacokinetic Analyses

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 may be performed as appropriate.

13.3.5. Interim Analyses

Due to an unanticipated delay in enrollment and study pause associated with the COVID-19 pandemic, as well as the elderly frail population, we are planning to conduct 1 or more unblinded analyses to evaluate the safety data (especially cardiovascular endpoints) to help guide dosing. In addition, we hope to gain further experience with regard to the endpoints under consideration, as many of the tools employed in this study are yet to be characterized in a shortened study of this nature.

Interim analyses are not anticipated for Part B of this study.

13.4. Sample Size Determination

[redacted]

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[redacted]

[redacted]

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[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 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

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

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

14.2. Site Initiation

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

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

14.3. Study Documents

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

14.3.1. Good Clinical Practice Documents

The GCP documents are listed below.

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

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

14.3.2. Case Report Forms

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

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

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

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

14.3.3. Source Documents

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

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

14.4. Data Quality Control

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

14.4.1. Monitoring Procedures

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

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

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

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

14.4.2. Data Management

The sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the sponsor's or contract research organization's (CRO) standard operating procedures. A comprehensive data management plan will be developed including a data management plan, database contents, annotated CRF, self-evident correction conventions, query contacts, and consistency checks.

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

14.4.3. Quality Assurance/Audit

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

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

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

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

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

14.5. Study Termination

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

14.5.1. Regular Study Termination

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

14.5.2. Premature Study Termination

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

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

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination visit.

14.6. Study Site Closure

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

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

14.6.1. Record Retention

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

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

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

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

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

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

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

14.6.2. Sample Retention

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

14.7. Changes to the Protocol

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

14.8. Use of Information

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

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

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.

17. REFERENCES

Alderfer BS, Allen MH. Treatment of Agitation in Bipolar Disorder Across the Life Cycle. J Clin Psychiatry. 2003; 64 (Suppl 4): 3-9.

Allen, M H, Currier, G W, Hughes, D H, Reyes-Harde, M, Docherty, J P. The Expert Consensus Guideline Series. Treatment of behavioral emergencies. Postgraduate medicine. 2001;(Spec No):1-88.

Allen MH, Currier GW, Hughes DH, Docherty JP, Carpenter D, Ross R. Treatment of Behavioral Emergencies: A Summary of the Expert Consensus Guidelines. Journal of Psychiatric Practice. 2003; 9: 16–38.

Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar P, Spyker DA, Cassella JV. Efficacy and Safety of Loxapine for Inhalation in the Treatment of Agitation in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Psychiatry. 2011: 72; 10: 1313-1321.

Battaglia J. Pharmacological Management of Acute Agitation. Drugs. 2005; 65 (9): 1207-1222.

Conn DK, Lieff S. Diagnosing and Managing Delirium in the Elderly. Can Fam Physician. 2001; 47: 101-108.

Currier GW, Trenton A. Pharmacological Treatment of Psychotic Agitation. CNS Drugs. 2002; 16 (4): 219-228.

Currier GW, Allen MH, Bunney EB, Daniel DG, Francis A, Jagoda A, Zimbroff D. Standard Therapies for Acute Agitation. Journal of Emergency Medicine. 2004; Vol. 27: S9–S12.

MHRA. CLH Report: Proposal for Harmonised Classification and Labelling, Substance Name: Medetomidine. October 2014. Version 1.

Oquendo MA, Halberstam B, Mann JJ. Colombia Suicide Severity Rating Scale (C-SSRS) – Risk Factors for Suicidal Behavior: The Utility and Limitations of Research Instruments, in Standardized Evaluation in Clinical Practice. First MB, editor. American Psychiatric Publishing; Washington, DC: 2003: 103-131.

Osser DN, Sigadel R, Short-Term Inpatient Pharmacotherapy of Schizophrenia. Harvard Review of Psychiatry. May-June 2001; Volume 9 (Issue 3): 89-104.

Salzman C, Jeste DV, Meyer RE, Cohen-Mansfield J, Cummings J, Grossberg GT, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: Consensus statement on treatment options, clinical trials methodology, and policy. Journal of Clinical Psychiatry. 2008, May 13; 69: 889-898.

Precedex. US Package Insert. 2016 May.

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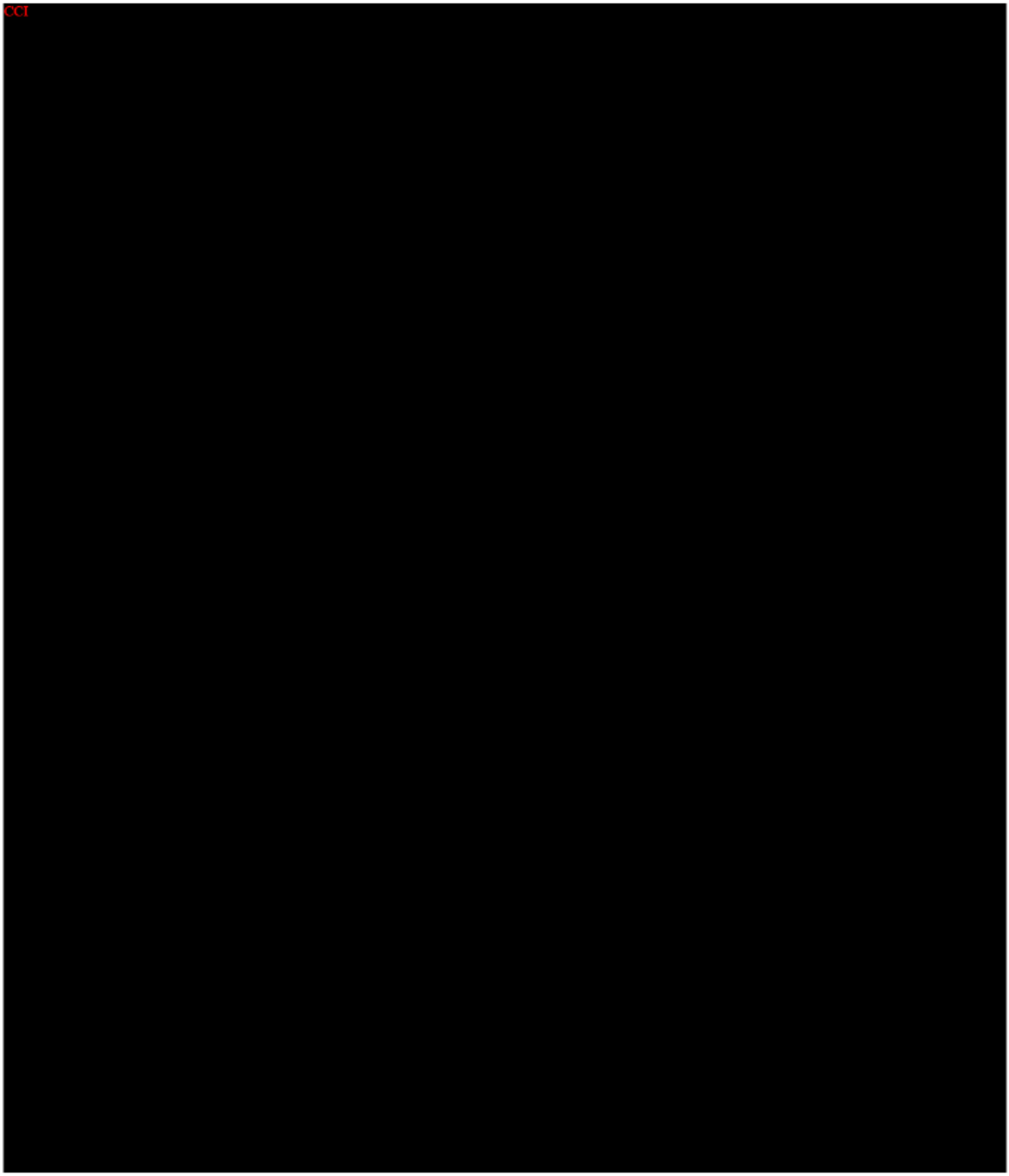

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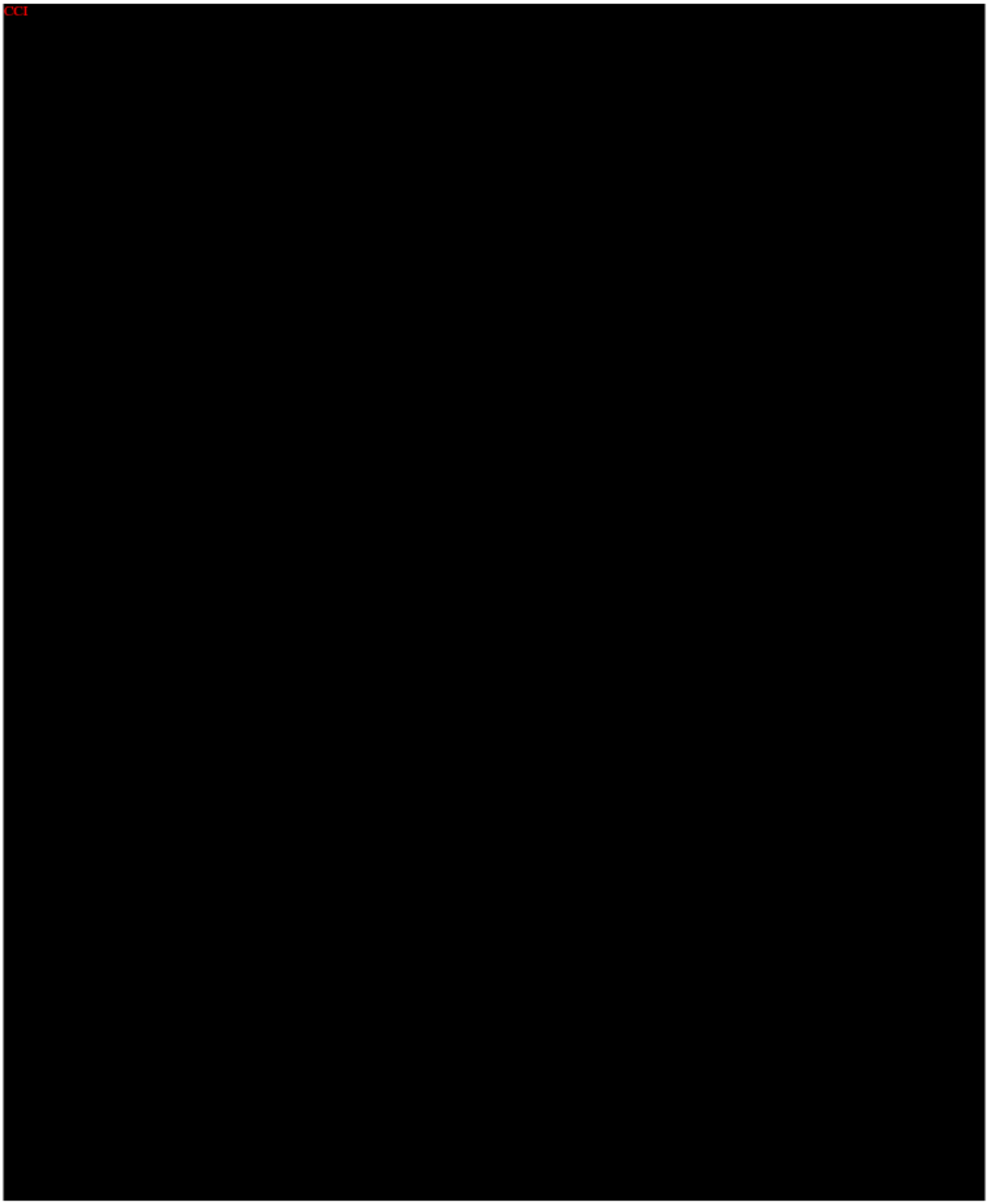

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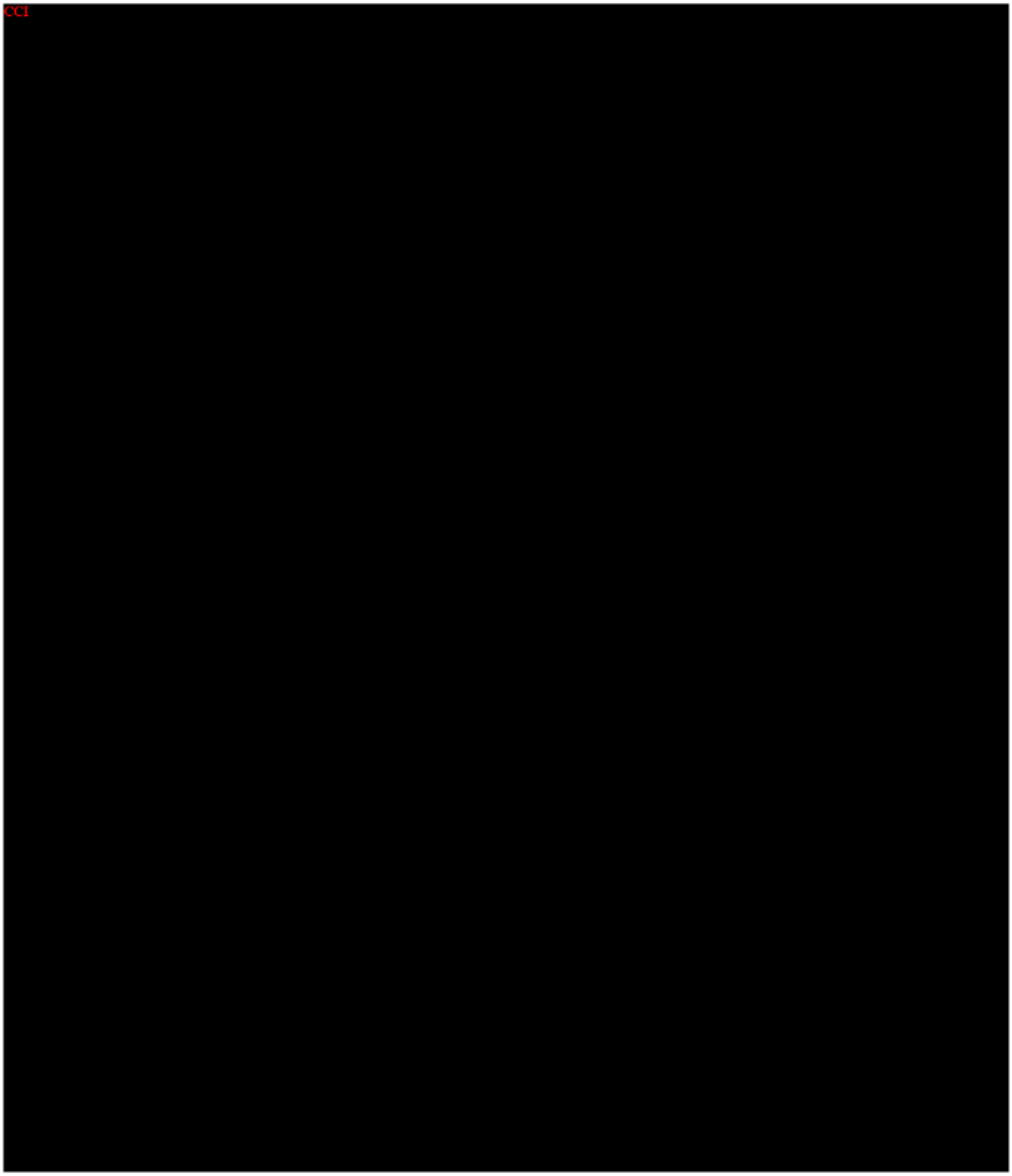

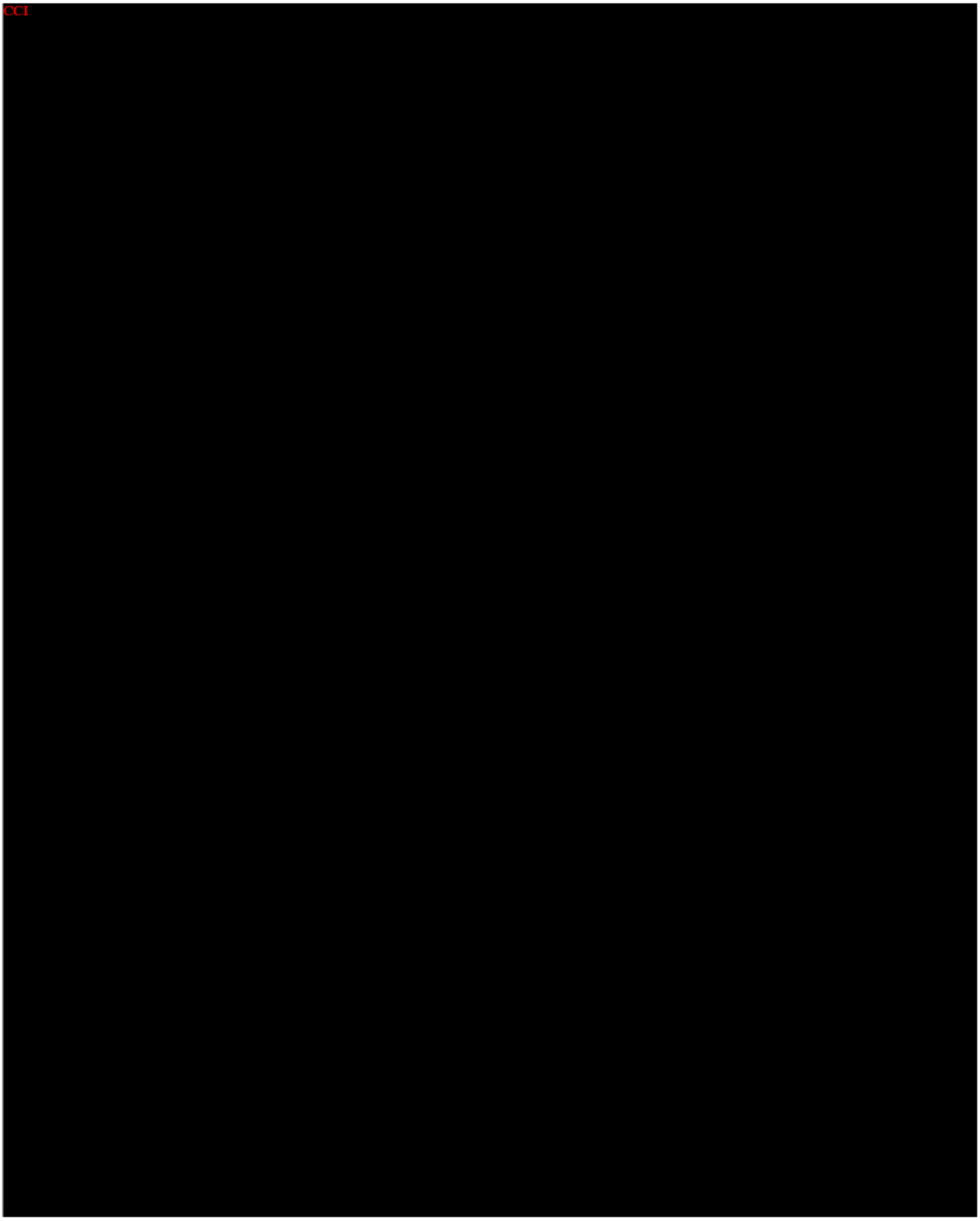
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