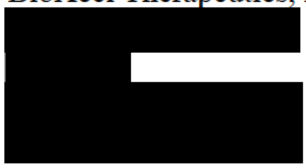
A Phase III Multicenter, Randomized, Double-blind, Placebo-controlled Study to Determine Efficacy and Safety of BXCL501 in Agitation Associated with Bipolar Dosorder

NCT04276883

01/31/2020

A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF BXCL501 IN AGITATION ASSOCIATED WITH BIPOLAR DISORDER

PROTOCOL NUMBER:	BXCL501-302
STUDY PHASE:	Phase 3
IND NUMBER:	140184
PROTOCOL VERSION:	3
PROTOCOL DATE:	20 SEP 2019
AMENDMENT 1 DATE:	16 DEC 2019
AMENDMENT 2 DATE:	31 JAN 2020
SPONSORED BY:	BioXcel Therapeutics, Inc.



PROTOCOL APPROVAL

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SPONSOR: BioXcel Therapeutics, Inc.

[redacted]

STUDY PRODUCT: BXCL501

Sponsor Approval:

Date: 1/31/20 Signature: [redacted]

1. PROCEDURES IN CASE OF EMERGENCY

Table 1.1: Sponsor/CRO Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted]	[redacted]
Clinical Operations Leader	[redacted]	[redacted]
Study Manager	[redacted]	[redacted]
Medical Monitor/24-hour Emergency Contact	[redacted]	[redacted]
	Secondary Contact: [redacted]	[redacted]

2. INVESTIGATOR AGREEMENT

PROTOCOL TITLE: A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF BXCL501 IN AGITATION ASSOCIATED WITH BIPOLAR DISORDER

PROTOCOL NUMBER: BXCL501-302

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: BXCL501-302

Title of study: A Phase III Multicenter, Randomized, Double-blind, Placebo-controlled Study to determine Efficacy and Safety of BXCL501 in Agitation associated with Bipolar Disorder

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

Phase of development: 3

Objectives:

Primary objective:

To determine if a single dose of BXCL501 effectively reduces symptoms of acute agitation associated with bipolar disorder assessed using the Positive and Negative Syndrome Scale – Excited Component (PEC) change from baseline as compared to placebo.

Key secondary objective:

To determine the earliest time where an effect on agitation is apparent as measured by the change from baseline in PEC total score.

Other exploratory objectives:

To further determine the efficacy, safety, tolerability and PK of BXCL501 in patients with acute agitation associated with bipolar disorder, including:

1. To determine the overall clinical improvement after drug administration as measured by the Clinical Global Impression – Improvement Scale (CGI-I).
2. Describe the duration of calming as measured by PEC and Agitation and Calmness Evaluation Scale (ACES).
3. Determine the safety profile of BXCL501 as measured by reports of adverse events and vital signs.
4. Describe the overall tolerability in terms of treatment-emergent adverse event reports and local site (oral/sublingual) tolerability of oral film.
5. Describe the subject's opinion on taste, acceptability, and likability of study medication.
6. Characterize the patient population utilizing the Young Mania Rating Scale (YMRS).

Study Design: This is a randomized, double-blind, placebo-controlled Phase III study assessing efficacy, safety and tolerability of BXCL501 dosing in adult (18-75 years old) males and females with acute agitation associated with bipolar disorder as defined by DSM-5 criteria.

This in-clinic study will randomize subjects 1:1:1 to receive BXCL501 (180µg or 120µg dose of DEX) or matching placebo film. The randomization will be stratified by age; age < 65 and age ≥ 65. Eligible subjects (acutely agitated subjects with bipolar disorder) may be identified in outpatient clinics, 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 hospitalized for chronic underlying conditions. Subjects will be domiciled in a clinical research setting or

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hospitalized to remain under medical supervision while undergoing screening procedures to assess eligibility. Upon confirmation of eligibility, subjects will be randomized to receive either 180µg BXCL501 or 120µg BXCL501 or matching placebo. At the time of dosing, patients will be instructed on how to take the investigational product sublingually, and that they should retain the investigational product in the sublingual cavity until dissolved. The patient will self-administer under the supervision of a trained staff member. If the patient is unable to self-administer, the event will be recorded, and the subject's participation will conclude. In the event of persistent or recurrent agitation, investigators may choose to repeat dose at 90µg or 60µg (half of 180 µg or 120µg film) after the 2-hour time point as measured by a PEC change from baseline ≤40% but in the absence of safety concerns. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than 90/60 systolic/diastolic) and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of > 20 mm Hg systolic, or 10 mm Hg diastolic) or if they are experiencing an AE that in the assessment of the PI precludes redosing. The maximum number of repeat doses per subject is 2, during the 12 hours post first dose. Doses may not be administered sooner than 2 hours after a previous dose. If the PEC change from baseline is >40% repeat dosing is not allowed. 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. All efforts should be made to have the patient perform all assessments as per protocol. However, should the patient's status warrant it, standard of care rescue treatment for agitation with lorazepam 0.5-5 mg po/IM may be initiated at any time, preferably after the 24-hour assessments are completed. Efficacy, safety, tolerability, and pharmacokinetics (PK) will be measured throughout the treatment period at various timepoints. Please refer to the Table 3.1 Schedule of events for details. Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on the final study day or upon early termination. For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be stable and no longer of clinical concern.
Number of subjects (planned): Approximately 375 subjects will be enrolled at up to 30 study sites in the United States.
Diagnosis and Main Criteria for Eligibility: *Inclusion Criteria* 1. Male and female patients between the ages of 18 to 75 years, inclusive. 2. Patients who have met DSM-5 criteria for bipolar I or II disorder. 3. Patients who are judged to be clinically agitated at Screening and Baseline with a total score of ≥ 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PANSS Excited Component (PEC).

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4. Patients who have a score of ≥ 4 on at least 1 of the 5 items on the PEC at Baseline.
5. Patients who read, understand and provide written informed consent.
6. Patients who are in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG with rhythm strip, blood chemistry profile, hematology, urinalysis, and in the opinion of the Principal Investigator.
7. Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agree to use a medically acceptable and effective birth control method throughout the study and for one week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include: the rhythm method, withdrawal, condoms alone, or diaphragm alone.

Exclusion Criteria

1. Patients with agitation caused by acute intoxication, including positive identification of alcohol by breathalyzer or drugs of abuse (with the exception of THC) during urine screening.
2. Use of benzodiazepines or other hypnotics or antipsychotic drugs in the 4 hours before study treatment.
3. Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
4. Patients judged to be at serious risk of suicide must be excluded.
5. Female patients who have a positive pregnancy test at screening or are breastfeeding.
6. Patients who have hydrocephalus, seizure disorder, or history of significant head trauma, stroke, transient ischemic attack, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, Parkinson's disease or focal neurological findings.
7. History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1, 3 and 5 min measurements), a screening and baseline heart rate of < 55 beats per minutes or systolic blood pressure <110 mmHg or diastolic BP <70 mmHg.
8. Patients with laboratory or ECG abnormalities considered clinically significant by the investigator or qualified designee [Advanced heart block (second-degree or above atrioventricular block without pacemaker), diagnosis of Sick sinus syndrome] that would have clinical implications for the patient's participation in the study.
9. Patients with serious or unstable medical illnesses. These include current hepatic (moderate-severe hepatic impairment), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease, congestive heart failure), endocrinologic, or hematologic disease.
10. Patients who have received an investigational drug within 30 days prior to the current agitation episode.

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11. Patients who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving DEX; e.g. patients with a history of allergic reactions to DEX.
Test Product, Dose, and Mode of Administration: BXCL501 is a thin film formulation of DEX for sublingual (SL) administration. Dosing delivers 180µg or 120µg of DEX sublingually. The product is a small, solid-dose film formulation, approximately 193.6 mm^2 in area and 0.7 mm thick, designed to completely dissolve in the SL space within 1-3 minutes.
Reference therapy, dosage and mode of Administration: Matching placebo films to be taken sublingually as described above.
Duration of Treatment: 1 day.
Criteria for Evaluation: ***Efficacy assessment:*** Assessment of Drug Effects on acute agitation will be done by 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. Overall agitation and sedation will be evaluated with the Agitation-Calmness Evaluation Scale (ACES), where 1 indicates marked agitation; 2 - moderate agitation; 3 - mild agitation; 4 - normal behavior; 5 - mild calmness; 6 - moderate calmness; 7 - marked calmness; 8 - deep sleep; and 9 – unarousable. The overall clinical improvement in agitation in response to treatment will also be measured by the Clinical Global Impressions – Improvement (CGI-I). 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. To characterize the patient population, manic symptoms will be assessed using the Young Mania Rating Scale (YMRS), an 11-item scale based on the patient's subjective report of their clinical condition. ***Safety and tolerability assessments:*** AEs, clinical laboratory tests, ECG with rhythm strip, pulse oximetry, and vital signs will be monitored for tolerability assessment. All observed and volunteered AEs will be recorded. The relationship of AEs to the study drug will be graded as not related, unlikely/remotely related, possibly related, probably related or definitely related by the investigators. Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate will be monitored. The application site of the SL preparation (buccal mucosa) will be inspected for any signs of local irritation. ***Additional Assessments:*** Demographics, Medical and Psychiatric History, Smoking history, Prior and Concomitant Medication, Physical Examination, Pregnancy. ***Pharmacokinetics:*** A sparse PK sampling of plasma concentrations at specified timepoints will be reported. A population PK/PD analysis of plasma concentration vs. clinical response will be reported

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using a separate SAP and report. A graphical assessment of PK vs. vital signs and other potential PD parameters will be included.

Statistical Analysis:

General: The null and alternative hypotheses to be tested are stated as H_{01}: $\Delta_{BXCL501\_180} = \Delta_{PBO}$ and H_{A1}: $\Delta_{BXCL501\_180} \neq \Delta_{PBO}$ and H_{02}: $\Delta_{BXCL501\_120} = \Delta_{PBO}$ and H_{A2}: $\Delta_{BXCL501\_120} \neq \Delta_{PBO}$, where $\Delta_{BXCL501\_180}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 180 µg group, $\Delta_{BXCL501\_180}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 180 µg group, $\Delta_{BXCL501\_120}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 120 µg group, and Δ_{PBO} denotes the change from baseline in the PEC at 2 hours post-dose in the placebo group. These hypotheses will be tested using a mixed model repeated measures (MMRM) model. To account for the testing of two hypotheses, the two-sided significance level for each test will be determined using the Bonferroni correction and set at 0.025.

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

Sample Size Determination: The power calculations for this study are based on the results of the Phase Ib study of BXCL501 (BXCL501-102; further described in Section 13.4). Based on the outcome of that study, a two-sided significance level of 0.025, 125 patients per treatment arm would provide 90% statistical power for the BXCL501/ placebo pairwise comparison for the primary efficacy endpoint (absolute change from baseline in the PEC total score at 2 hours post-dose) with a minimum detectable difference of approximately 2.1 units or larger in the change from baseline in the PEC total score.

A blinded sample size recalculation will take place when approximately 50% of the information is available. The pooled standard deviation of the change from baseline in PEC total score will be computed at each time point. The sample size will then be recalculated with the potential to increase the sample size accordingly.

Table 3.1: Schedule of Events

			Treatment Evaluation Day 1												
Activity	**Screening**	**Pre-Dose[1]**	**Post Dose Time[1]**										**Day 2 Follow-Up (+1)**	**Day 3 Discharge**	**Day 7 (+2)**
Time point	**Pre-treatment**	**-1 hr to time 0**	**10 min**	**20 min**	**30 min**	**45 min**	**1 hr**	**1.5 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**24 hr (-9/+12 hr)**		**End of Study**
Informed Consent	X														
Medical History	X														
Demographics	X														
Weight	X												X		
Height	X														
BMI	X														
Alcohol Breathalyzer	X														
MINI	X														
Physical Exam	X												X		
Safety Labs[2]	X													X	X
ECG with rhythm strip [3]	X	X							X				X		
Pulse oximetry		X			X		X		X	X		X			
Resting vital signs[4]	X	X			X		X		X	X	X	X	X	X	X
Orthostatic vital signs[4]	X	X							X	X		X	X	X	X
Admit to Unit	X														
Inclusion/Exclusion criteria	X	X													
Randomization		X													
Study drug administration[9]		X													
YMRS		X											X		
PCRS[5]	X	X							X				X		
PEC[5]	X	X	X	X	X	X	X	X	X	X	X	X	X		
ACES[5]		X							X	X		X			
CGI-Severity[6]	X	X													
CGI-Improvement[6]					X		X		X	X					

			Treatment Evaluation Day 1												
Activity	**Screening**	**Pre-Dose[1]**	**Post Dose Time[1]**										**Day 2 Follow-Up (+1)**	**Day 3 Discharge**	**Day 7 (+2)**
Time point	**Pre-treatment**	**-1 hr to time 0**	**10 min**	**20 min**	**30 min**	**45 min**	**1 hr**	**1.5 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**24 hr (-9/+12 hr)**		**End of Study**
C-SSRS	X	X											X	X	
Buccal (SL) assessment for local irritation[7]					X				X	X			X		
Likert Scales				X											
Likability Questions				X											
Pharmacokinetic Sampling[8]							X			X		X			
Concomitant Meds	X	X	X										X	X	X
Adverse Events	X	X	X										X	X	X

Notes to the Schedule of Events:

[1] Pre-dose assessments will have a window of 60 minutes prior to dose with the exception of PEC and ACES which will be performed within 15 minutes of dosing (15 to 0 min). All post-dose assessments will have a window of -5/+15 minutes through the 1.5 hour assessments, -5/+25 minutes for the 2 hour assessments (with the exception of the PEC which will have a +/-5 minute window) and ± 30 minutes for the 4, 6 and 8 hour assessments and YMRS can be performed at any time.

[2] Safety Labs will include chemistry, hematology, urinalysis, UDS (local lab, only conducted at screening), alcohol breathalyzer (only conducted at screening), and urine pregnancy (only conducted at screening). Screening/enrollment labs: local labs drawn within 7 days prior to screening may suffice with the exception of urine drug screen. If results not available on the same day, a 'desktop' or non-CLIA test may be performed; to confirm, results from a CLIA-certified laboratory should be recorded once available. Central Labs should be performed on Screening, Day 3 and Day 7.

[3] ECG for pre-dose does not need to be repeated if screening ECG is conducted on the day of dosing. ECGs collected following treatment are to be performed prior to PK assessments.

[4] Resting (recumbent) vital signs (SBP, DBP and HR) will be taken upon having the subject recumbent for 5 min at Screening, Pre-dose and at 30 min, 1, 2, 4, 6, 8 and 24 hours post dose, as well as Day 3 and Day 7. Triplicate measurements to be performed in case of Systolic BP <90 mmHg, Diastolic BP <60 mmHg or Pulse < 60 bpm. Orthostatic measurements (SBP, DBP, HR, respiratory rate) will be taken upon having the subject stand, with measurements taken after 1,3 and 5 minutes and temperature will be taken at Screening, Pre-dose, 2, 4, 8 and 24 hours post first dose, as well as Day 3 and Day 7.

[5] PEC will be performed at Screening, Pre-dose (within 15 min prior to dose) and at 10, 20, 30, 45 min; 1, 1.5, 2, 4, 6, 8 and 24 hours post dose. The PCRS must be performed prior to PEC rating, when required. ACES will be performed at Pre-dose (within 15 min of dose), 2, 4 and 8 hrs post dose.

[6] CGI-Severity will be performed at Screening and pre-dose. CGI-Improvement will be performed at 30 minutes, 1, 2 and 4 hours post dose.

[7] Buccal exam at 30 min, 2, 4 and 24hr post-dose for local irritation.

[8] PK blood samples will be collected 1, 4, and 8 hr (while awake) after dose. A sample may not be collected if the Physician indicates in source documents that the patient is in a mental state that is not conducive to PK sample collection. Non-compliance or refusal of all or any PK draw will not be exclusionary nor result in ET. Vital signs are to be done prior to PK sample draws, when performed at the same timepoints.

[9] The investigator may choose to re-dose the patient after the 2 hour post-dose assessments are performed if the PEC change from baseline is $\leq$ 40%. Patients can be re-dosed after completing the 2 hour post first dose assessments. Repeat dosing administers half of a film. Patients can be redosed twice in the 12 hour period post first dose . All assessments listed in this Schedule of Events at the 2 hour post first dose timepoint should be repeated at 2 hours post every re-dose. Assessments at 4, 6, or 8 hour post first dose that occur within 1 hour of a post re-dose assessment are not required to be performed.

4. TABLE OF CONTENTS

4.1 List of Tables

5. LIST OF ABBREVIATIONS AND DEFINTIONS 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
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CLIA	Clinical Laboratory Improvement Amendments
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
Dex or DEX	Dexmedetomidine
DLT	Dose Limiting Toxicity
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ET	Early Termination
FDA	US Food and Drug Administration
FD&C	United States Federal Food, Drug, and Cosmetic Act
g	gram
GABA	Gamma-Amino Butyric Acid

Abbreviation	Definition
GCP	Good Clinical Practices
HCl	Hydrochloride
HR	Heart rate
hr	hour
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent To Treat
IUD	Intrauterine Device
IV	Intravenous
kg	kilogram
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	millimeters
mmHG	millimeters of mercury
MMRM	Mixed model repeated measures
MS	Mass spectrometry
MTD	Maximum tolerated dose
MW	Molecular weight
PANSS-EC	Positive and Negative Syndrome Scale – Excited Component
PCRS	Placebo-Control Reminder Script
PD	Pharmacodynamics
PEC	Positive and Negative Syndrome Scale – Excited Component

Abbreviation	Definition
pg	picogram
pH	measure of hydrogen ion concentration
PI	Principal Investigator
PK	Pharmacokinetic
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
USP	United States Pharmacopeia
YMRS	Young Mania Rating Scale

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 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 onset of action after both oral and intramuscular administration is typically 30-60 min due to slow absorption into the systemic circulation. Slow onset of action extends suffering of agitated patients and increases the need for physical restraint or seclusion (Allen et al. 2003).

In contrast to oral or IM administration, intravenous injection (IV) results in onset of anti-agitation action within 1-5 min (Allen et al. 2001, 2003). However, it is generally impractical to use IV administration in agitated patients. 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 the most important factor in selecting an agitation treatment. The discrepancy between the need for speed of onset in treatment of agitation and the slow onset of most frequently utilized treatments represents a substantial unmet medical need in the population of patients with behavioral emergencies. An alternative non-invasive yet rapidly delivered 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). By controlling norepinephrine release from the locus coeruleus, BXCL501 has a novel mode of action compared to current therapies (D2 antagonists and GABA agonists) and is previously untested for the treatment of acute agitation. In addition, because it enters the blood stream directly by the sublingual route and bypasses first-pass metabolism in the 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 with substantial bioavailability via the oral mucosal route and no route-specific safety signals (oral mucosal or gastrointestinal).

BXCL501 is a sublingual thin film formulation of dexmedetomidine which is intended for the acute treatment of agitation. BXCL501 is designed as a self-administered discrete low dose film with mucoadhesive properties. It is therefore expected that its administration in agitated patients

will lead to faster onset of clinical response than administration of oral or intramuscular preparations.

BXCL501 was evaluated for PK, bioavailability and safety in a randomized, double-blind, placebo-controlled trial. Doses from 10 to 40 µg (Study BXCL501-101) in healthy volunteers produced lower systemic exposure (Cmax and AUCs) compared to the PK parameters presented in the Precedex package insert and was safe and well tolerated. Sedation as measured by visual analog scale and other measures were similar for BXCL501 in contrast with placebo at each dose level; while there was a greater incidence of arousable sedation for the highest dose tested. Cardiovascular activity was monitored with relatively few incidents of bradycardia, hypotension or orthostatic hypotension that were either non-reproducible or generally mild and transient.

A multicenter, double-blind, placebo-controlled, Phase 1b trial (Study BXCL501) was conducted in agitated subjects with schizophrenia to evaluate the safety and efficacy BXCL501. Subject self-administration of BXCL501, with doses ranging from 20 to 180µg, was associated with a safe, well-tolerated and effective calming as measured by a reduction in PEC scores at 2 hours. Preliminary results of the BXCL501-102 study suggested calming effects as measured by group mean reduction from baseline PEC score achieving statistically significant separation from placebo as early as 45 min, at 2 hr and maintained through 6 hrs and longer. There were no SAEs and treatment-emergent AEs were generally transient, mild to moderate in severity. The most commonly reported AEs were arousable, intermittent somnolence (of mild to moderate severity) and dry mouth. There were no clinically meaningful changes in cardiovascular parameters in the 180µg dose group and no medical interventions were necessary.

Agitation can be seen in different bipolar disorders but is predominantly associated with bipolar I disorder and is less frequently observed in bipolar II disorder. This study will enroll subjects with agitation associated with bipolar I or II disorder. Bipolar disorder, as defined by DSM-5, is subdivided into distinct disorders, the most common being bipolar I disorder, or bipolar II disorder. Bipolar I disorder is associated with at least one full episode of mania and possible additional episodes of full depression, occurring later in time or concurrently (“mixed episodes”). Bipolar II disorder is characterized by at least one episode of hypomania and at least one episode of major depression. Episodes in bipolar I and II disorders may be recurrent and progress in severity over time.

As noted previously, agitation is a common occurrence in multiple psychiatric disorders, and while the etiology of agitation is not fully understood, hypothesized dysfunctions in norepinephrine, dopamine, serotonin and GABA systems are consistent with the demonstrated efficacy of agents such as benzodiazepines and typical and atypical antipsychotics (Lindenmayer, 2000; Battaglia 2005; Berk 2005). In recent years, formulations of the atypical antipsychotics Zyprexa (Meehan, 2001), Geodon (Bellnier, 2002), and Abilify (Sanford, 2008) for intramuscular injection have received FDA approval for treating agitation in patients with bipolar I disorder with mania or mixed episodes (with or without psychotic features), as well as approval for treating agitation in patients with schizophrenia. The schizophrenia and bipolar disorder studies have generally utilized similar clinical trial designs to evaluate the efficacy and safety of these agents over a 24 hour period following intramuscular injection. Furthermore, for each agent, similar efficacious dose ranges were approved for treating agitation in bipolar disorder and schizophrenia.

Study Rationale

The purpose of the present Phase 3 study is to assess the safety and efficacy of BXCL501 in the treatment of acute agitation in patients with bipolar I or II disorder with hypomania, mania or mixed episodes and to assess the safety and tolerability over a 24-hour period. The study will be conducted in patients who are either newly admitted to a hospital setting or a research unit for acute agitation, or already in-hospital for the treatment of bipolar disorder. Patients meeting entry criteria will be randomized to 180µg BXCL501 or 120µg BXCL501 or to matching placebo. Following administration of study drug, assessment of agitation will be conducted at serial time points using standard agitation scales over a 24-hour period. The PANSS Excited Component (PEC) scale will be the primary efficacy measure.

6.2 Description

Dexmedetomidine hydrochloride is the active S-enantiomer of medetomidine. BXCL501 is a sublingual film comprised of dexmedetomidine and the following inactive ingredients: Polyethylene Oxide, Hydroxypropyl Cellulose, Sucralose, Peppermint Oil, Emerald Green colorant, and FD&C Blue #1 colorant.

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

7. OBJECTIVES

7.1 Primary Endpoint

The primary efficacy endpoint of the study will be the absolute change from baseline in the PEC total score at 2 hours. The intent to treat population will be analyzed and consists 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).

7.2 Key Secondary Endpoint:

The key secondary efficacy endpoint will be the earliest time where an effect on agitation is apparent as measured by change from baseline PEC total score in contrast with placebo.

Exploratory endpoints include:

1. Overall clinical improvement after drug administration as measured by the Clinical Global Impression – Improvement Scale (CGI-I) score.
2. Agitation-Calmness Evaluation Scale (ACES) scores at 2, 4 and 8 hrs after dose administration.
3. Change from baseline in total PEC score over time measured from 10 min through 24 hrs after dosing.
4. PEC Responders and CGI-I Responders at 2 hours following dose of BXCL501, compared with placebo:
    a. PEC responders will be defined as those who achieve at least a 40% reduction in PEC total score from baseline at or before 2 hours post-dose.
    b. CGI-I responders will be defined as subjects with a score of 1 or 2 on the CGI-I scale (the CGI-I non-responders will be defined as subjects with scores from 3 to 7 at 2 hours).
5. Time to rescue medication during the entire 24 hrs Post-treatment Evaluation Period for subjects receiving BXCL501 compared to placebo.
6. Proportion of subjects per treatment group who received rescue medication by 4 hrs and within 24 hrs after dosing.
7. Duration of calming effect as described by the change from baseline in PEC total score, and ACES score at 2, 4 and 8 hrs after dosing.
8. Determine the safety profile of BXCL501 as measured by vital signs and treatment-emergent adverse event reports.
9. Describe the overall tolerability in terms of adverse event reports and local site (oral/sublingual) tolerability of oral film.
10. Descriptive pharmacokinetics of BXCL501 in the patient population.
11. Determine patient acceptability, taste and likability of study medication using likert scales to capture subject's acceptability, opinion on taste and questions regarding likability.
12. Characterize the patient population utilizing the Young Mania Rating Scale (YMRS).

8. STUDY DESIGN

8.1 Overall Study Design and Plan

The study will enroll approximately 375 subjects randomized 1:1:1 to dose regimens of 180µg, 120µg BXCL501, or placebo stratified by age < 65 and age ≥ 65. The doses were selected based on the results of the prior Phase Ib clinical trial (Study BXCL501-102).

Male and female adults with acute agitation associated with bipolar I or II disorder will be enrolled.

Eligible subjects (acutely agitated subjects with bipolar I or II disorder) may be identified in outpatient clinics, 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 be domiciled in a clinical research setting or hospitalized to remain under medical supervision while undergoing screening procedures to assess eligibility.

Upon confirmation of eligibility, subjects will be randomized to 180µg BXCL501 or 120µg BXCL501 or matching placebo. Efficacy and safety assessments will be conducted periodically before and after dosing.

Vital Signs, pulse oximetry and ECG with rhythm strip will be measured as per schedule of assessments, prior to any PK assessments. Participants will be allowed water as desired 15 minutes after completion of dosing. Safety and tolerability assessments will be conducted at various timepoints. Please refer to the Table 3.1 Schedule of events for details.

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

Approximately 4 mL of venous blood (to obtain a minimum of 1.2 mL plasma) will be taken into K2-EDTA tubes at set time intervals for the determination of plasma concentrations of study drug (or Placebo). The PK plasma samples should be collected within 10 min of the scheduled sampling time on Day 1. Blood samples will be collected per Table 3-1 Schedule of Events.

8.2 Discussion of Study Design

This is a definitive study to support the safety and efficacy evaluation of BXCL501 for the acute treatment of agitation in bipolar disorder. The BXCL501-302 study is designed to characterize the efficacy, safety and tolerability of BXCL501 (sublingual film formulation of DEX, HCl) in agitation associated with bipolar disorder. A dose of BXCL501 was chosen based on results from BXCL501-102 that showed rapid efficacy in a large proportion of subjects, was well tolerated and had an acceptable safety profile. In the event of persistent or recurrent agitation, investigators may choose to repeat dose at 90µg or 60µg (half of 180µg or 120µg film) after the 2-hour time point as measured by a PEC change from baseline ≤40% but in the absence of safety concerns. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than 90/60 systolic/diastolic) and not bradycardic (must be greater than 60

bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of > 20 mm Hg systolic, or 10 mm Hg diastolic) or if they are experiencing an AE that in the assessment of the PI precludes redosing.. The maximum number of repeat doses per subject is 2, during the 12 hours post first dose. Doses may not be administered sooner than 2 hours after a previous dose. If the PEC change from baseline is >40% repeat dosing is not allowed.

Placebo was chosen as a comparator to more accurately assess efficacy as well as safety and tolerability. The randomized, double blind parallel-group design ensures the sponsor, all subjects, and study staff involved are shielded from treatment assignment and outcomes and therefore will minimize any potential bias. The randomization ratio provides an additional element to ensure blinding by decreasing the odds of guessing treatment arms.

8.3 Study Sites

The study will take place at up to 30 sites in the US.

9. SUBJECT POPULATION

9.1 Selection of Study Population

9.2 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 between the ages of 18 to 75 years, inclusive.
2. Patients who have met DSM-5 criteria for bipolar I or II disorder.
3. Patients who are judged to be clinically agitated at Screening and Baseline with a total score of ≥ 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PANSS Excited Component (PEC).
4. Patients who have a score of ≥ 4 on at least 1 of the 5 items on the PEC at Baseline.
5. Patients who read, understand, and provide written informed consent.
6. Patients who are in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG with rhythm strip, blood chemistry profile, hematology, urinalysis, and in the opinion of the Principal Investigator.
7. Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agree to use a medically acceptable and effective birth control method throughout the study and for one week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods include: the rhythm method, withdrawal, condoms alone, or diaphragm alone.

9.3 Exclusion Criteria

A subject will be excluded from the study if he or she meets the following criteria:

1. Patients with agitation caused by acute intoxication, including positive identification of alcohol by breathalyzer or drugs of abuse (with the exception of THC) during urine screening.
2. Use of benzodiazepines, other hypnotics or antipsychotic drugs in the 4 hours before study treatment.
3. Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
4. Patients judged to be at serious risk of suicide must be excluded.
5. Female patients who have a positive pregnancy test at screening or are breastfeeding.
6. Patients who have hydrocephalus, seizure disorder, or history of significant head trauma, stroke, transient ischemic attack, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, Parkinson's disease or focal neurological findings.

7. History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1, 3 and 5 min measurements), a screening and baseline heart rate of < 55 beats per minutes or systolic blood pressure <110 mmHg or diastolic BP <70 mmHg.
8. Patients with laboratory or ECG abnormalities considered clinically significant by the investigator or qualified designee [Advanced heart block (second-degree or above atrioventricular block without pacemaker), diagnosis of Sick sinus syndrome] that would have clinical implications for the patient's participation in the study.
9. Patients with serious or unstable medical illnesses. These include current hepatic (moderate-severe hepatic impairment), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease, congestive heart failure), endocrinologic, or hematologic disease.
10. Patients who have received an investigational drug within 30 days prior to the current agitation episode.
11. Patients who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving DEX; e.g. patients with a history of allergic reactions to DEX.

9.4 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 that is intolerable to the subject or otherwise considered unacceptable, for intolerable 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, subjects will be randomized to 180µg BXCL501 or 120µg BXCL501 or placebo.

Randomization will be 1:1:1 (180µg or 120µg BXCL501 or Placebo and stratified by age < 65, age ≥ 65) with 125 patients assigned to each arm by a permuted block design. Study randomization will be computer generated.

10.2 Identification of Investigational Product

BXCL501 will be provided as a small, solid-dose film formulation, approximately 193.6 mm^2 in area and 0.7 mm thick, designed to completely dissolve in the SL space within 1-3 min.

BXCL501 Sublingual Film 180µg, 120µg and placebo will be packaged as individual films in a heat-sealed white foil pouch with a drug product label. The pouch has a white colored outer layer with foil colored inner layer. Individual film appearance is as follows:

- 180µg – Green rectangular thin film (~22 mm x 8.8 mm)
- 120µg – Green rectangular thin film (~22 mm x 8.8 mm)
- Placebo – Green rectangular thin film (~22 mm x 8.8 mm)

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

10.3 Treatment Administration

At the time of dosing, patients will be instructed on how to take the investigational product sublingually, and that they should retain the investigational product in the sublingual cavity until dissolved. The patient will self-administer under the supervision of a trained staff member. If the patient is unable to self-administer, the event will be recorded, and the subject's participation will conclude.

In the event of persistent or recurrent agitation, investigators may choose to re-dose at 90µg or 60µg (cutting half of the 180µg or 120µg film) after the 2-hour time point as measured by a PEC change from baseline ≤40% but in the absence of safety concerns.

10.4 Storage

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

10.5 Labeling

Each pouch 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 to the subjects for self-administration under the supervision of a trained staff member.

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 Treatment Compliance

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

10.9 Concomitant Medications

All concomitant medications administered (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.

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 or designee, 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 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 hrs after dosing of study treatment and the indication (Insomnia) must be clearly recorded in CRF and source documents.

Prohibited Therapies

The following medications are prohibited in the 4 hours before dosing of study treatment:

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 the time of screening until 4 hours post last dose, unless clinically indicated:

Antiarrhythmics, Antibiotics/antifungals/antivirals, Anticholinergics, Anticonvulsants, Antipsychotics, Antihypertensive, Anxiolytics or sedative-hypnotics, Centrally acting calcium antagonist, Cholinomimetics, Migraine-Serotonin Receptor Agonist, Opioids.

11. STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of concomitant therapy.

The schedule of events to be performed during the study is provided in Table 3.1.

11.1 Screening

Subjects must be 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 Screening (refer to the Schedule of Events table):

- Obtain written informed consent
- Review inclusion and exclusion criteria
- Collect demographic information
- Record medical history, including prior and current therapies (e.g. prescription and non-prescription medications)
- Physical examination including weight, height, body mass index, and vital signs
- Urine pregnancy test for all females of childbearing potential
- 12-lead ECG with rhythm strip
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen)
- Alcohol breathalyzer
- MINI
- Placebo-Control Reminder Script (PCRS) (prior to PEC)
- PEC
- CGI-S
- C-SSRS
- Adverse events are recorded following informed consent
- Record concomitant medication use
- Admit to Clinical Research Unit (for subjects not currently admitted)

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.

11.2 Day 1, Pre-Dose

The following procedures will be performed prior to dosing:

- Review inclusion and exclusion criteria
- Assess and record AEs
- Record concomitant medication use
- Resting (recumbent) and Orthostatic Vital signs
- Pulse Oximetry
- ECG with rhythm strip (not required if screening ECG is conducted on the day of dosing)
- C-SSRS
- YMRS
- CGI-S
- Randomization
- Placebo-Control Reminder Script (PCRS) (prior to PEC)
- PEC (within 15 min of dosing)
- ACES (within 15 min of dosing)

Upon completion of the pre-randomization procedures, the subject will be randomized to study treatment (180µg BXCL501 or 120µg BXCL501 or placebo), study drug administration will occur, and the following procedures will be performed (Refer to the Schedule of Events for specific time points):

11.3 Day 1, Post-Dose Assessments

- CGI-I
- PCRS (prior to PEC)
- PEC
- ACES
- Vital Signs (Resting/Recumbent and Orthostatic)
- ECG with rhythm strip
- Pulse oximetry
- Buccal (SL) Assessment
- Likert scales
- Likability Questions
- Assess and record AEs
- Record concomitant medication use
- Plasma sample 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.

Investigators may choose to repeat dosing with the 90µg or 60µg dose (half of 180µg or 120µg film) after the 2-hour time point for persistent or recurrent agitation (PEC change from baseline ≤40%) but only in the absence of safety concerns. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than 90/60 systolic/diastolic) and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of > 20 mm Hg systolic, or 10 mm Hg diastolic) or if they are experiencing an AE that when assessed by the PI precludes redosing. All 2 hour assessments (including efficacy and safety) must be completed before repeat dosing may occur. The maximum number of repeat doses allowed per subject is 2, during the 12 hours post first dose. Doses may not be administered sooner than 2 hours after a previous dose. If the PEC change from baseline is >40% repeat dosing is not allowed. As noted in the Schedule of Events (Table 3.1), all assessments listed at the 2-hour post first dose timepoint should be repeated at 2 hours post every re-dose.

11.4 Day 2 (+1), Follow Up

The following procedures will be performed on Day 2:

- ECG with rhythm strip
- Physical exam including weight
- Resting/Recumbent and Orthostatic Vital sign and weight measurements
- YMRS
- PCRS (prior to PEC)
- PEC
- C-SSRS
- Buccal (SL) Assessment
- Record concomitant medication use
- Assess and record AEs

11.5 Day 3, Discharge

The following procedures will be performed on Day 3, Discharge:

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Resting/Recumbent and Orthostatic Vital signs
- C-SSRS
- Record concomitant medication use
- Assess and record AEs

The protocol permits a maximum 3 overnight stays from allowed admission to the Clinical Research Unit to Discharge. If more nights are required, Medical Monitor approval is required.

11.6 Day 7 (+2)

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

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Resting/Recumbent and Orthostatic Vital signs
- 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.

PANSS – Excitatory 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.

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.

CGI-S and CGI-I

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 illness will be assessed based on following scale:

0 = Not assessed

1 = Not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

Drug response on agitation will be evaluated by the Clinical Global Impressions – Improvement (CGI-I). It will be performed at 30 minutes, 1, 2 and 4 hrs post dose. The CGI-I scores range from 1 to 7:

0=not assessed (missing),

1=very much improved,

2=much improved,

3=minimally improved,

4=no change,

5=minimally worse,

6=much worse,

7=very much worse

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

Young Mania Rating Scale (YMRS)

The YMRS is an 11-item scale evaluating mania symptoms based on the patient's subjective report of their clinical condition. It will be used to characterize the patient population enrolled in the study.

Placebo-Control Reminder Script (PCRS)

The Placebo-Control Reminder Script (PCRS) © Hassman and Cohen, 2019, Version 5.0 educates clinical trial participants of key causes of the placebo and nocebo effects, namely the tempering of participant study expectations, reminding subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with previous providers. To do this, the PCRS informs subjects that they are to be honest about their symptoms, site staff have no expectations of symptom improvement or worsening and will not be disappointed if they feel better, worse or the same, and asks participants to explain in their own words its content to ensure comprehension. The PEC Rater will read the PCRS study source before administering the PEC to EACH subject at EACH Visit (time point) listed on the study specific PCRS, typically taking about 2 minutes to read.

Likert scales

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

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

Drug likability

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

12.2 Pharmacokinetics

Blood samples (4 ml) will be collected per Table 3-1 Schedule of Events. A sample may not be collected if the physician indicates in the source documents that the patient is in a mental state that is not conducive to PK sample collection.

For each subject, up to 3 blood samples (12 mL of blood) will be collected during the study for PK analysis. In addition, approximately 30 mL of blood will be collected at screening, approximately 15 mL of blood will be collected at Day 3 Discharge, and approximately 15 mL of blood will be collected at Day 7(+2) for clinical laboratory testing. The total volume of blood collected during the study is expected to be approximately 72 mL. Whenever possible for all SAEs a blood sample for PK analysis will be drawn to evaluate a potential relationship with exposure.

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 eight (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 1500g 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.

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 - 60°C to - 80°C freezer until shipment. 20°C freezers can also be used for a short period of time (maximum one month) until they are shipped to the bioanalytical laboratory.

Sample Shipment

- Prior to shipment, the samples will be appropriately packed into a Styrofoam cooler containing dry ice.
- Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 72 hours for remote shipments.

- Samples will be shipped in two aliquots. The second set will be shipped once the status of the first set has been verified.
- The site staff will maintain an inventory of the samples that are to be shipped to the bioanalytical laboratory, including the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. A copy of the inventory will accompany the frozen PK samples.
- The samples will be tracked to ensure arrival in a safe and timely manner.
- Samples will be shipped to:

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

Analytical Procedures

12.2.1.1 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 one 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.

12.2.1.2 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.

12.3 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.

An independent data safety monitoring board (DSMB) will be chartered to review all SAEs and AE reports while the study remains blinded to the sponsor. The DSMB will meet regularly to evaluate the safety data. Should a known safety issue be identified (e.g. a high incidence of severe hypotension or bradycardia in the active 180µg dose arm or the 120µg arm), the DSMB

will notify the sponsor. Should this occur, sponsor will notify FDA, and sponsor may choose to continue dosing the patients at a lower dose.

Adverse Events

12.3.1.1 Adverse Event Definitions

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

Preexisting 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.

12.3.1.2 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 consent 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.

12.3.1.3 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 Med DRA 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 12.3.1.1) 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: Safety@bioxceltherapeutics.com and Cognitive Research Corporation: ekemper@cogres.com

12.3.1.3.1 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. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

12.3.1.3.2 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 sufficient 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.

12.3.1.3.3 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.

12.3.1.4 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.

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

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).

Local Labs (Screening only: To determine subject eligibility):

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 for females of childbearing potential only (local only)
Urine Drug Screen:	Cocaine, amphetamine, phencyclidine, benzodiazepines, marijuana. (Note; marijuana positive is allowed provided subject is not moderately to severely dependent, benzodiazepine positive are allowed if prescribed)
Alcohol breathalyzer:	Only conducted at screening

Central Labs (Screening, Day 3 and Day 7):

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

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 (Table 3.1). Measurements should be made at least 1 minute apart using the same arm at each visit.

At indicated timepoints orthostatic measurement of systolic, diastolic blood pressure, and heart rate will be measured after the subject has been standing for a total 1, 3 and 5 minutes at the time points specified in the schedule of events (Table 3.1). 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

Electrocardiogram

A 12-lead ECG with rhythm strip will be performed at Screening, Pre-dose, 2, and 24 hours post dose and 2 hours post any re-dose. Date and time of ECG, ventricular heart rate (beats/minute), P-R Interval, QRS Duration, QT Interval (msec) will be collected. QTcF (msec) will be calculated.

Pulse Oximetry

Pulse oximetry will be performed at pre-dose and repeated 30 mins, 1, 2, 4, and 8 hours post dose. (Table 3.1)

Physical Examination

A standard physical examination will be performed at 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 Screening and weight will be measured again at the Day of discharge. BMI will be calculated and recorded.

Concomitant Medications

Concomitant medications will be reviewed and documented during each study visit.

Likert scales

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

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

Drug likability

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

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.

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 post-dose;
- 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 will be imputed using multiple imputation. As the prior studies had little missing data, it is anticipated that methods for monotone missing data will be used with values imputed as needed. Efficacy analyses and summaries will be presented for both the ITT Population and the PP Population, with the former being primary. Details of the statistical analyses will be provided in the Statistical Analysis Plan which will be finalized prior to database lock.

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.

Efficacy Analyses

The primary efficacy endpoint of the study will be the absolute change from baseline in the PEC total score at 120 min. The intent to treat 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 null and alternative hypotheses to be tested are stated as H_{01}: $\Delta_{BXCL501\_180} = \Delta_{PBO}$ and H_{A1}: $\Delta_{BXCL501\_180} \neq \Delta_{PBO}$ and H_{02}: $\Delta_{BXCL501\_120} = \Delta_{PBO}$ and H_{A2}: $\Delta_{BXCL501\_120} \neq \Delta_{PBO}$, where $\Delta_{BXCL501\_180}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 180 µg group, $\Delta_{BXCL501\_180}$ denotes the change from baseline in the PEC at 2 hours post-dose in the BXCL501 180 µg group, $\Delta_{BXCL501\_120}$ denotes the change from baseline in the PEC at 2 hours

post-dose in the BXCL501 120 µg group, and Δ_{PBO} denotes the change from baseline in the PEC at 2 hours post-dose in the placebo group. These hypotheses, H_{01} and H_{02}, will be tested using a mixed model repeated measures (MMRM) model. To account for the testing of two hypotheses, the two-sided significance level for each test will be determined using the Bonferroni correction and set at 0.025. The outcome variable for the MMRM will be the change from baseline in the PEC score at 10, 20, 30, 45, 60, 90, and 120 minutes and the following set of covariates: treatment group, baseline PEC, visit, baseline PEC by visit interaction term, and treatment group by visit interaction term. The test of the null hypothesis is obtained from a least squares mean analysis. A sensitivity analysis will be conducted to assess the impact of any missing data. Control-based, multiple imputation will be used to impute missing values based on the placebo group experience, with details of the sensitivity analysis provided in the SAP.

The key secondary endpoints will be evaluated using the fixed-sequence method with the endpoints ordered in a hierarchy within each dosing group comparison with testing stopping once a significance level is greater than 0.025. The key secondary endpoints are as follows:

1. Change from baseline in the PEC score at 90 minutes.
2. Change from baseline in the PEC score at 60 minutes.
3. Change from baseline in the PEC score at 45 minutes.
4. Change from baseline in the PEC score at 30 minutes.
5. Change from baseline in the PEC score at 20 minutes.
6. Change from baseline in the PEC score at 10 minutes.

Other exploratory endpoints include:

1. Overall clinical improvement after drug administration as measured by the Clinical Global Impression – Improvement Scale (CGI-I) score
2. Agitation-Calmness Evaluation Scale (ACES) scores at 2, 4 and 8 hrs after dose administration.
3. Change from baseline in total PEC score over time measured from 10 min through 24 hrs after dosing.
4. PEC Responders and CGI-I Responders at 2 hours following dose of BXCL501, compared with placebo:
    a. PEC responders will be defined as those who achieve at least a 40% reduction in PEC total score from baseline at or before 2 hours post-dose.
    b. CGI-I responders will be defined as subjects with a score of 1 or 2 on the CGI-I scale (the CGI-I non-responders will be defined as subjects with scores from 3 to 7 at 2 hours).
5. Time to rescue medication during the entire 24 hrs Post-treatment Evaluation Period for subjects receiving BXCL501 compared to placebo.
6. Number of subjects per treatment group who received rescue medication by 4 hrs and within 24 hrs after dosing.
7. Duration of calming effect as described by the change from baseline in PEC total score at 4, 6, 8 and 24 hrs after dosing.
8. Determine the safety profile of BXCL501 as measured by vital signs and treatment-emergent adverse event reports and vital signs.

9. Describe the overall tolerability in terms of adverse event reports and local site (oral/sublingual) tolerability of oral film.
10. Descriptive pharmacokinetics of BXCL501 in the patient population.
11. Determine patient acceptability, taste and likability of study medication using Likert scales to capture subject's acceptability, opinion on taste and questions regarding likability.
12. Characterize the patient population utilizing the Young Mania Rating Scale (YMRS).

The exploratory outcomes will be analyzed using a variety of techniques depending on the outcome and including two-sample t-tests, Fisher's exact test, Kaplan-Meier curves for time-to-event outcomes and descriptive methods such as box plots, frequency distributions and shift tables. All significance levels will be reported as nominal levels.

Safety Analyses

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

Adverse events (AEs) will be characterized by type, severity, seriousness, and relationship to treatment. Adverse events will be coded by preferred term and system organ class using MedDRA version 20.0. 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 sign, ECG with rhythm strip, and clinical laboratory results will be summarized by treatment. Physical examination findings will be listed.

Pharmacokinetic Analyses

Plasma concentrations and concentration-time data for dexmedetomidine will be used to calculate PK parameters; these data and results will be reported separately. Details regarding the analyses of PK data will be described in a separate PK SAP. The separate SAP for the PK analyses will be prepared and finalized prior to database lock. Data from subjects who participated in the study will be included in the pharmacokinetic analysis. Subjects with missing sample concentrations will be included in the pharmacokinetic analyses provided their pharmacokinetic 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 pharmacokinetic data from the analyses for a particular subject. This includes any deviations or events that would invalidate the evaluation of the pharmacokinetics. Examples of deviations and events which could result in exclusion of pharmacokinetic 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 pharmacokinetic parameters will be calculated using non-compartmental analysis using WinNonlin Version 5.2 or higher. Actual sampling times will be used in all pharmacokinetic analyses. Per protocol times will be used to calculate mean plasma concentrations for graphical displays.

Other PK analyses may be performed as appropriate.

13.4 Sample Size Determination

The estimated sample size was estimated using information from the Phase 2 study regarding the standard deviation of the change from baseline in PEC score and the expected magnitude of this difference. Under the assumptions of a two-sided significance level of 0.025, a two-sample t-test, a randomization ratio of 1:1, an assumed power of 0.90, and standard deviations of 4.0, 4.2, 4.4, and 4.6. The estimated sample size per group is provided in Table 13.1 below. Table 13.12 provides the estimated sample size per group for a power of 0.85. The observed difference between the BXCL501 and placebo groups in the 180µg group was 0.7, 3.5, 5.0, 6.0, and 6.2 at 30, 45, 60, 90, and 120 minutes, respectively. With a sample size of approximately 375 subjects (125/group) the study is well powered to detect differences at 45 minutes or later.

A blinded sample size recalculation will take place when approximately 50% of the information is available. The pooled standard deviation of the change from baseline in PEC total score will be computed at each time point. The sample size will then be recalculated with the potential to adjust the sample size accordingly.

Table 13.1: Estimated Sample Size group for power of 0.90

Estimated sample size/group for power of 0.90, a two-sided significance level of 0.025, varying mean difference in change from baseline in PEC score, and standard deviations of the change from baseline in PEC score.

	Standard deviation			
Mean difference	4.0	4.2	4.4	4.6
2.0	101	111	122	133
1.9	112	123	135	147
1.8	124	137	150	164
1.7	139	153	168	184

Table 13.2: Estimated Sample Size group for power of 0.85

Estimated sample size/group for power of 0.85, a two-sided significance level of 0.025, varying mean difference in change from baseline in PEC score, and standard deviations of the change from baseline in PEC score.

	Standard deviation			
Mean difference	4.0	4.2	4.4	4.6
2.0	88	97	106	115
1.9	97	107	117	128
1.8	108	119	130	142
1.7	121	133	146	159

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

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 sufficient material and support to permit the investigator to conduct the study according to the study protocol.

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 Conference on 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. Confidentiality of records identifying the subject will be maintained. The Food and Drug Administration may inspect the records at any time.

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
- 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.

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.

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.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.4 Data Quality Control

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

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.

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.

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.

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.

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, applicable regulations and guidelines, or both;
- Inadequate subject enrollment.

Record Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study. All records and documents pertaining to the study including, but not limited to those defined by GCP as essential will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the drug.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution when these documents no longer need to be retained. To avoid any possible errors, the Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in the event of accidental loss or destruction of any study records.

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 study report to the regulatory authorities by the sponsor.

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 study report will be written according to the "Guideline for Industry (Structure and Content of Clinical Study Reports)" from the International Conference on Harmonisation (ICH) E3. The final study report will present a narrative description of the clinical, analytical, pharmacokinetic, 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 before any activity or procedure is undertaken that is not part of routine care.

16.3 Approval by Institutional Review Board

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

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

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

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