CHARACTERIZATION OF TACHYPHYLAXIS, TOLERANCE, AND WITHDRAWAL AFTER DISCONTINUATION OF IGALMI IN FREQUENTLY AGITATED SCHIZOPHRENIC OR BIPOLAR PATIENTS AFTER 7 DAYS OF PRN TREATMENT

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CHARACTERIZATION OF TACHYPHYLAXIS, TOLERANCE, AND WITHDRAWAL AFTER DISCONTINUATION OF IGALMI IN FREQUENTLY AGITATED SCHIZOPHRENIC OR BIPOLAR PATIENTS AFTER 7 DAYS OF PRN TREATMENT

PROTOCOL NUMBER:	BXCL501-404
STUDY PHASE:	Phase 4
IND NUMBER:	140184
PROTOCOL VERSION:	Version 6.0
PROTOCOL DATE:	16DEC2022
AMENDMENT 1:	09MAR2023
AMENDMENT 2:	18MAY2023
AMENDMENT 3:	06JUN2023
AMENDMENT 4:	10AUG2023
AMENDMENT 5:	26OCT2023

SPONSORED BY: BioXcel Therapeutics, Inc.
555 Long Wharf Drive
12th Floor
New Haven, CT 06511
Phone: [redacted]

PROTOCOL APPROVAL

CHARACTERIZATION OF TACHYPHYLAXIS, TOLERANCE, AND WITHDRAWAL AFTER DISCONTINUATION OF IGALMI IN FREQUENTLY AGITATED SCHIZOPHRENIC OR BIPOLAR PATIENTS AFTER 7 DAYS OF PRN TREATMENT

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SPONSOR:	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 U.S.A.
STUDY PRODUCT:	IGALMI™ (dexmedetomidine) sublingual film

Sponsor Approval:

Date: _____ Signature: _____

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 30-Oct-2023 | 3:56:05 PM EDT
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[redacted], MD
Medical Monitor

1. PROCEDURES IN CASE OF EMERGENCY

Table 1.1: Sponsor/CRO Contact Information

Role in Study	Name	Address and Telephone Number
Project Manager	[redacted]	Lotus Clinical Research, LLC 430 Mountain Ave #302 New Providence, NJ 07974 Phone: [redacted]
Director, Project Management	[redacted]	Lotus Clinical Research, LLC 430 Mountain Ave #302 New Providence, NJ 07974 Phone: [redacted]
Medical Monitor/24-hour Emergency Contact	[redacted], MD	Lotus Clinical Research, LLC 430 Mountain Ave #302 New Providence, NJ 07974 [redacted]
	Secondary Contact: [redacted], MD	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 Telephone: [redacted] Cell: [redacted] [redacted]

2. INVESTIGATOR AGREEMENT

PROTOCOL TITLE: CHARACTERIZATION OF TACHYPHYLAXIS, TOLERANCE, AND WITHDRAWAL AFTER DISCONTINUATION OF IGALMI IN FREQUENTLY AGITATED SCHIZOPHRENIC OR BIPOLAR PATIENTS AFTER 7 DAYS OF PRN TREATMENT

PROTOCOL NUMBER: BXCL501-404

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., Lotus Clinical Research, LLC, 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: IGALMI™ (dexmedetomidine) sublingual film

Name of active ingredient: Dexmedetomidine (DEX)

Protocol number: BXCL501-404

Title of Study: CHARACTERIZATION OF TACHYPHYLAXIS, TOLERANCE, AND WITHDRAWAL AFTER DISCONTINUATION OF IGALMI IN FREQUENTLY AGITATED SCHIZOPHRENIC OR BIPOLAR PATIENTS AFTER 7 DAYS OF PRN TREATMENT

Estimated number of trial center(s): Multicenter (3 sites)

Phase of development: Post-Marketing Commitment

Objectives:

Primary objective:

- Characterize tachyphylaxis, tolerance and withdrawal after 7 days of PRN treatment with IGALMI™ (dexmedetomidine) sublingual for agitation associated with schizophrenia or bipolar disorder

Secondary objective:

- Determine the safety and tolerability of IGALMI under the studied dosing conditions

Rationale:

Many drugs, when dosed repeatedly, lose effectiveness. This phenomenon is called tachyphylaxis when it occurs rapidly (within hours) or tolerance when it occurs more gradually (over days). Withdrawal occurs when the body adapts to repeated exposure to a drug and then administration of that drug is abruptly stopped. For example, it might be expected that after repeated exposure to dexmedetomidine, a drug that lowers blood pressure, stopping administration might cause rebound hypertension. Because previous studies with IGALMI were conducted with single doses, or in populations that experience highly infrequent episodes of agitation, there is little to no data on whether dexmedetomidine is associated with tolerance or withdrawal following repeated frequent dosing. To assess these phenomena, BioXcel proposes to administer IGALMI to a patient population selected for exhibiting frequent, near daily, episodes of agitation.

In response to the FDA request to examine the potential for tachyphylaxis, tolerance and withdrawal associated with IGALMI, BioXcel is planning to study withdrawal, tachyphylaxis, and tolerance after dosing as needed (PRN) for 7 days in subjects with bipolar disorder or schizophrenia who are agitated frequently (at least 3 days a week) in an inpatient setting. This 7-day treatment period will be followed by a 3- day follow up period during which time no IGALMI will be administered in an effort to characterize any potential withdrawal.

Name of sponsor/company: BioXcel Therapeutics, Inc.
Name of investigational product: IGALMI™ (dexmedetomidine) sublingual film
Name of active ingredient: Dexmedetomidine (DEX)
Protocol number: BXCL501-404
Study Design: This is an in-clinic, single arm, open label study assessing tachyphylaxis/tolerance and withdrawal following repeated doses of IGALMI™ (dexmedetomidine) sublingual film in adult males and females (18 to ≤ 65 years old) with agitation associated with schizophrenia or bipolar disorder. Subjects will be screened for eligibility within 15 days of first dose and no study procedures will occur unless subjects provide written informed consent. Subjects will sublingually self-administer IGALMI after receiving instructions and under the supervision of staff 180 µg will be administered for an agitation episode that reaches a pre-dose PEC criterion of 14 or greater, as determined by a trained rater. The film will be retained in the sublingual cavity until dissolved. Subjects will also be periodically evaluated for local irritation around the area where the film is placed. Safety assessments will be conducted before and after each dose. All efforts should be made to have the subject perform all assessments as per protocol. If the subject's agitation is recurrent or persistent, repeat doses of 90 µg may be administered (no more than 2 repeat doses within a 12-hour period) in the absence of any safety concerns or adverse events. Should the subject's status warrant it, standard of care rescue treatment for agitation can also be initiated, preferably after the post dose 2-hour assessments are completed. Safety, tolerability, and efficacy will be measured throughout the treatment period. Safety and tolerability assessments including vital signs will be monitored pre-dose and post-dose for each dose administered. Any abnormal vital sign measurement or physical examination finding deemed clinically significant by the investigator will be repeated and followed to resolution. All subjects will receive single doses of 180 µg of IGALMI as needed for the treatment of agitation over a period of 7 days. As noted above, in the event of persistent or recurrent agitation, investigators may choose to repeat dose at 90 µg after the 2-hour time point in the absence of dose-limiting adverse events or safety concerns. A maximum of 2 repeat doses will be allowed in a 12-hour period. ***Follow-up:*** Safety and tolerability will be monitored during the follow up period of 3 days post last dose (Day 7). Hemodynamic parameters and AEs will be recorded in addition to any agitation episodes that occur during follow up. During follow up period, agitation episodes will be rated pre-dose using the PEC scale but not treated with IGALMI, rather, during the follow up period, subjects will be treated with their standard of care (SOC).
Number of subjects (planned): Approximately 20 subjects will be enrolled at approximately 3 trial sites in the United States.

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Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

1. Male and female subjects between the ages of 18 to ≤ 65 years.
2. Subjects who have met DSM-5 criteria for schizophrenia, schizoaffective, or schizophreniform disorder or bipolar I or II disorder.
3. Subjects who are judged to be clinically agitated at pre-dose with a total score of ≥ 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the Positive and Negative Syndrome Scale - Excited Component (PEC).
4. Subjects who are currently moderate to severely agitated at least 3 days a week.
5. Subjects who read, understand, and provide written informed consent.
6. Subjects who are in good general health prior to study participation as determined by a detailed medical history and in the opinion of the Principal Investigator.
7. Female subjects, 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.
8. Subjects must be willing to remain in-clinic for the duration of the study.
9. Subjects must have been taking medication for the treatment of schizophrenia or bipolar disorder for at least 30 days prior to screening.

Exclusion Criteria

1. Subjects 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, barbiturates, antihistamines, sedating antidepressants, triptans, opioids, antipsychotics, and antihypertensives in the 4 hours before study treatment.
3. Subjects with congenital prolonged QT syndrome.

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4. Prior treatment with IGALMI. 5. Suicidality as assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). A score of ≥4 on the Ideational Component in the last year is exclusionary. Clinically significant risk of suicide based on the Investigator's clinical opinion or a history of an actual suicide attempt in the last year are also exclusionary; or self-injurious behavior that is active. 6. Female subjects who have a positive pregnancy test at baseline or are breastfeeding. 7. Subjects 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. 8. History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1, 3 and 5 min measurements), a pre-dose heart rate of < 55 beats per minutes or systolic blood pressure <110 mmHg or diastolic BP <70 mmHg. 9. Subjects with clinical 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. 10. Subjects 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. 11. Subjects who have received an investigational drug within 30 days prior to the current agitation episode. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving DEX; e.g. subjects with a history of allergic reactions to DEX.
Test Product, Dose, and Mode of Administration: IGALMI will be provided as a thin, solid-dose film formulation of dexmedetomidine, designed to dissolve in the sublingual (SL) space. Dosing delivers 180 µg sublingually.
Duration of Study: 10 days (7 days of PRN treatment with IGALMI and 3 days of follow up)
Endpoints: Primary Endpoints:

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• PEC reduction from pre-dose to 2 hours post-dose (i.e., change from pre-dose) and CGI-I Score at 2 hours post dose for all doses administered. Secondary Endpoint: • Withdrawal phenomenon based on adverse events and hemodynamic effects during the 3-day follow-up assessed as the percentage of subjects observed with the occurrence of AEs including tachycardia, systolic hypertension, nausea, or vomiting and the emergence of any new AEs on ≥2 consecutive days of the 3-day off treatment period. Exploratory Endpoints: • Percentage of PEC responders after the first dose compared to the percentage of responders after the last dose. Responders are those with at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment. • Percentage of CGI-I responders after the first dose compared to the percentage of responders after the last dose. Responders are those with a CGI-I score of 1 or 2 at 2 hours post-dose of study treatment. • CGI-S scores at pre-dose and change in CGI-S scores from baseline for all doses administered.
Criteria for Evaluation: ***Efficacy assessments:*** 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. The overall clinical improvement in agitation in response to treatment will also be measured by the Clinical Global Impression – 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. The severity of agitation will be measured by the Clinical Global Impression-Severity (CGI-S). CGI-S scores range from 0 to 4; 0 = not assessed (missing), 1=normal not at all symptomatic, 2 = Mildly symptomatic-low level of symptoms-little interference in social functioning, 3 = Moderately symptomatic-some prominent symptoms-some interference in functioning, 4= Severely symptomatic- very marked symptoms make it difficult for subjects to engage with others. ***Safety and tolerability assessments:*** AEs 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

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pressure (SBP), diastolic blood pressure (DBP), and heart rate), ECG data, and Agitation-Calmness Evaluation Scale (ACES) scores will be monitored. The application site of the SL preparation 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
Statistical Analysis: Analyses will be descriptive in nature and no inferential statistics will be applied. Analyses will be conducted on all subjects receiving at least one dose of study drug, unless otherwise specified. Summary statistics (n, mean, standard deviation, median, minimum, and maximum values) for actual values and change from baseline and/or pre-dose will be provided for continuous variables. Number and percentage of subjects in each category will be provided for categorical variables. Plots of individual subject values over time will be provided. As appropriate, additional figures may be created to supplement any of the analyses.
Tachyphylaxis/Tolerance assessment: For those subjects who receive at least one dose of study drug and have a PEC Score post-dose, PEC scores will be summarized by observed and change from baseline and pre-dose values using descriptive statistics. Observed CGI-I and observed and change from baseline CGI-S will be summarized descriptively. Number and percentage of PEC and CGI-I responders for each treated episode will be summarized. PEC responders are those with at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment. CGI-I responders are those with a CGI-I score of 1 or 2 at 2 hours post-dose of study treatment. ***Withdrawal assessment:*** The occurrence of withdrawal in an individual subject will be described as the occurrence of adverse events including tachycardia, systolic hypertension, nausea, or vomiting and the emergence of any new AEs on ≥2 consecutive days of the 3-day off treatment period. Data listings for subjects meeting withdrawal criteria will be provided and the number and percentage of subjects meeting withdrawal criteria will be summarized. ***Safety and Tolerability:*** The number and percentage of subjects experiencing 1 or more AEs will be summarized overall, by relationship to study drug and severity. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Listings of subjects who experience withdrawal due to an AE, serious AE and/or death will be presented. Vital signs, ECG data, and ACES scores will be summarized by change from baseline and/or pre-dose values using descriptive statistics.

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Sample Size Determination: The sample size is based on clinical experience and judgment relative to study design and objectives. Given the clinical data available to date for IGALMI, and the nature of this exploratory study a sample size of at least 20 subjects on active drug should provide adequate clinical information to meet the objectives of the study.

Table 3.1: Schedule of Events

Activity	*Screening (Within 15 days of first dose)	Days 1 – 7 PRN Dosing (Per Episode)		Follow Up/Early Termination[11]
Time point		**Pre-Dose**	**2 hrs Post-Dose (+/- 30 mins)**	**Days 8 – 10**
Informed consent	X			
Medical history	X			
Inclusion/Exclusion criteria	X	X		
Demographics	X			
Height	X			
Weight and BMI	X			
Physical exam	X			
Neurological exam	X			
Safety laboratory assessments	X[1]			
Urine Pregnancy Test (females of childbearing potential)	X	X[2]		
UDS and Breathalyzer	X[1]	X[2]		
Resting vital signs	X	X[3]	X	X[3]
Orthostatic vital signs[9, 10]	X	X[3]	X	X[3]
Heart Rate	X	X[3]	X	X[3]
ECG	X		X[4]	X[5]
Trial drug administration		X		
PEC		X[6]	X	X[7]
CGI-S		X		
CGI-I			X	
ACES		X[8]	X	
C-SSRS	X			
Concomitant medications	X	X	X	X
Adverse events	X	X	X	X

Notes to the Pre-First-and Post-Dose Schedule of Events:

***Screening (Within 15 days of first dose):** if no agitation episode occurs within 15 days subject can be re-screened only once. If after the re-screen, another 15 days has passed without a dosing episode, then the patient will be deemed a screen fail. If re-screen occurs greater than 30 days from Screening visit, all Screening assessments must be completed. If less than 30 days, re-screen assessments will be completed on a case-by-case basis with PI and Sponsor discretion.

[1] Safety labs and UDS results must be available prior to dosing.

[2]Urine Pregnancy Test, UDS and Breathalyzer conducted on Day 1 pre-dose first agitation episode only.

[3] Resting vital signs, orthostatic vital signs, and heart rate will be taken prior to agitation episodes if possible. Even if subject does not have an agitation episode during Follow Up/Early Termination, resting vital signs, orthostatic vital signs, and heart rate must be collected daily during this period.

[4] ECG to be performed 2 hours post first dose only on Day1.

[5] ECG to be performed during follow up/Early Termination period regardless if subject had an agitation episode. If subject was dosed on Day 7 ECG should be collected at least 24 hours post their last dose on Day 7.

[6] PEC will be conducted within 15 minutes of dosing.

[7] PEC ratings during 3 day Follow Up/ Days 8 – 10/ Early Termination will be collected before and after dosing with the subjects' standard of care medication at the time of an agitation episode.

[8] ACES will be conducted within 15 minutes prior to dosing.

[9] Temperature and respiratory rate will be recorded at the time of "resting" (i.e.: supine) vital signs measurement and are not required to be measured at each of the subsequent "orthostatic" (i.e.: sitting / standing) vital sign timepoints.

[10] "Orthostatic" vitals are the values obtained for blood pressure and heart rate with the patient in the sitting / standing position. "Resting" vitals are the values obtained for all vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the patient in the supine position.

[11] Follow-Up / Early Termination period will follow the same time window (both pre- and post-dose) as days 1-7.

4. TABLE OF CONTENTS

4.1. List of Tables

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ACES	Agitation-Calmness Evaluation Scale
BID	Twice daily
BP	Blood pressure
BMI	Body Mass Index
C	Celsius/Centigrade
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DBP	Diastolic blood pressure
Dex or DEX	Dexmedetomidine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EEG	Electroencephalogram
ET	Early Termination
FDA	US Food and Drug Administration
FD&C	United States Federal Food, Drug, and Cosmetic Act
g	gram
GCP	Good Clinical Practices
HR	Heart rate
hr	hour
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IM	Intramuscular

Abbreviation	Definition
IP	Intraperitoneal
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minutes
mm	millimeters
mmHg	millimeters of mercury
µg	microgram
n	Number
PEC	Positive and Negative Syndrome Scale – Excited Component
pH	Measure of hydrogen ion concentration
PI	Principal Investigator
po	oral/by mouth
PRN	As needed
RR	Response Rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SL	Sublingual
SOC	Standard of care
TEAE	Treatment emergent adverse event
THC	Tetrahydrocannabinol
UDS	Urine Drug Screen
US	United States of America

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 (Porsteinsson and Antonsdottir 2017), 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).

IGALMI is currently approved in the US as the sublingual formulation, Igalmi® (BioXcel US Package Insert 2022), for the acute treatment of agitation associated with schizophrenia and bipolar I and II disorders. Dexmedetomidine is also 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 by direct absorption into the blood through the oral mucosal route and no route-specific safety signals (oral mucosal or gastrointestinal). IGALMI is designed as a self-administered discrete low dose film with mucoadhesive properties.

Clinical Experience

IGALMI has been evaluated in multiple completed clinical trials in healthy volunteers and in agitated patients with schizophrenia or bipolar I or II disorder or dementia and for the mitigation of withdrawal symptoms following abrupt discontinuation of opioids. In these trials, more than 800 subjects have received doses of 10 µg to 480 µg /day. The Phase 3 clinical trials (BXCL501-301 and BXCL501-302) demonstrated that a single sublingual dose of IGALMI at 180 µg or 120 µg effectively and rapidly reduced the severity of an acute agitation episode in subjects with schizophrenia or schizoaffective disorder and subjects with bipolar disorder. The safety data collected in this trial showed that IGALMI at 180 µg and 120 µg was generally well tolerated and had a favorable safety profile in the treatment of subjects with agitation. The TEAEs reported in this trial were consistent with known common side effects of dexmedetomidine, namely dry mouth, bradycardia, hypotension, and somnolence.

Additionally, there are ongoing trials for IGALMI), including a trial in children with either schizophrenia or bipolar disorder who have episodes of agitation (BXCL501-105) and one completed trial for the treatment of agitation in subjects with dementia (BXCL501-303). IGALMI is also being evaluated in 7-day multiple ascending dose trial in healthy volunteers (BXCL501-106) to support repeat dosing in other indications.

Tachyphylaxis, Tolerance, and Withdrawal

There has not been evidence of tachyphylaxis, tolerance, or withdrawal in preclinical or clinical studies with BXCL501. In preclinical studies, rat EEG showed no evidence of tachyphylaxis or tolerance to daily IP dexmedetomidine over 3 weeks. The first dose and 21st consecutive days dose showed no difference in EEG effects in rat. Additionally, toxicology data with twice daily dose administrations at maximum tolerated doses that produce much greater exposure to

dexmedetomidine than the human exposure from the approved label dosing of IGALMI have not demonstrated tachyphylaxis for sedation.

Studies of prolonged high-dose, constant-rate IV exposure of dexmedetomidine (Precedex) to maintain sedation or treat delirium have been performed. In many of these studies, there is no evidence of tolerance or withdrawal after cessation of drug administration (Shehabi et al., 2004; Shehabi et al., 2019). However, in some case studies, some evidence for withdrawal and tolerance was reported (Burbano et al., 2012; Bouajramet et al., 2019). Unfortunately, these uncontrolled retrospective studies often confuse recurrence of the condition (like agitation) to be withdrawal effects and even support this assertion, claiming reversibility by substituting another alpha-2 agonist as proof. It is difficult to differentiate between re-emergence of the underlying agitation when treatment from dexmedetomidine is stopped from withdrawal effects. Lastly, although BioXcel has not specifically analyzed for evidence of tolerance or tachyphylaxis, we have studied doses of 240 μg BID for a total of 480 μg daily for one week in opiate withdrawal with no evidence of tachyphylaxis/tolerance or withdrawal by AE report or CV effects. While not definitive, it is suggestive that high doses of IGALMI are not associated with robust tolerance or withdrawal.

Study Rationale

In response to the FDA request to examine the potential for tachyphylaxis, tolerance and withdrawal associated with IGALMI, BioXcel is planning to study withdrawal, tachyphylaxis, tolerance after dosing as needed (PRN) for 7 days in subjects with bipolar disorder or schizophrenia who are agitated frequently (at least 3 days a week) in an inpatient setting. This 7-day treatment period will be followed by a 3 day follow up period during which time no IGALMI will be administered in an effort to characterize any potential withdrawal.

6.2. Description

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

No special transport or storage conditions are required for IGALMI. Packaged films should be stored at 20°-25°C (68°-77 °F) with excursions permitted between 15°-30°C (59°-86°F).

7. OBJECTIVES AND ENDPOINTS

7.1. Primary Objective

To characterize tachyphylaxis, tolerance and withdrawal after 7 days of PRN treatment with IGALMI for agitation associated with schizophrenia or bipolar disorder.

7.1.1. Endpoints in support of Primary Objective

- Primary Endpoint #1: Positive and Negative Syndrome Scale – Excited Component (PEC) reduction from pre-dose to 2 hours post-dose for all doses administered.
- Primary Endpoint #2: Clinical Global Impression-Improvement (CGI-I) at 2 hours post-dose for all doses administered.
- Secondary Endpoint: Withdrawal phenomenon based on adverse events (AEs) and hemodynamic effects during the 3-day follow-up assessed as the percentage of subjects observed with the occurrence of AEs including tachycardia, systolic hypertension, nausea, or vomiting and the emergence of any new AEs on ≥2 consecutive days of the 3-day off treatment period.
- Exploratory Endpoint #1: Percentage of PEC responders after the first dose compared to the percentage of responders after the last dose. Responders are those with at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment.
- Exploratory Endpoint #2: Percentage of Clinical Global Impression-Improvement (CGI-I) responders after the first dose compared to the percentage of responders after the last dose. Responders are those with a CGI-I score of 1 or 2 at 2 hours post-dose of study treatment.
- Exploratory Endpoint #3: Clinical Global Impression-Severity (CGI-S) at pre-dose and change from baseline for all doses administered.

7.2. Secondary Objective

To determine the safety and tolerability of IGALMI under the studied dosing conditions.

7.2.1. Endpoints in support of Secondary Objective

- Occurrence of AEs
- Observed, change from baseline, and change from pre-dose in vital signs
-
- Observed and change from baseline in 12-lead electrocardiograms (ECGs) parameters, and overall assessment
- Observed, change from baseline, and change from pre-dose in Agitation-Calmness Evaluation Scale (ACES)

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is an in-clinic, single arm, open label study assessing tachyphylaxis/tolerance and withdrawal following repeated doses of IGALMI in adult males and females (18 to ≤ 65 years old) with agitation associated with schizophrenia or bipolar disorder. Subjects will be screened for eligibility within 15 days of first dose and no study procedures will occur unless subjects provide written informed consent. Subjects must remain in-clinic during screening period and throughout the duration of the study.

Subjects will self-administer IGALMI 180 µg for an agitation episode that reaches a pre-dose PEC criterion of 14 or greater, as determined by a trained rater. IGALMI 180 µg film will be self-administered sublingually by the subject, after receiving instructions and under the supervision of staff. The film will be retained in the sublingual cavity until dissolved. Subjects will also be periodically evaluated for local irritation around the area where the film is placed. Safety assessments will be conducted before and after each dose. All efforts should be made to have the subject perform all assessments as per protocol. If the subject's agitation is recurrent or persistent, repeat doses of 90 µg may be administered (no more than 2 doses within a 12-hour period) in the absence of any safety concerns or adverse events. Should the subject's status warrant it, standard of care rescue treatment for agitation can also be initiated, preferably after the post dose 2-hour assessments are completed.

Safety, tolerability, and efficacy will be measured throughout the treatment period. Safety and tolerability assessments including vital signs will be monitored pre-dose and post-dose for each dose administered. Any abnormal vital sign measurement or physical examination finding deemed clinically significant by the investigator will be repeated.

All subjects will receive single doses of 180 µg of IGALMI as needed for the treatment of agitation over a period of 7 days. As noted above, in the event of persistent or recurrent agitation, investigators may choose to repeat dose at 90 µg after the 2-hour time point in the absence of dose-limiting adverse events or safety concerns. A maximum of 2 re-doses will be allowed in a 12-hour period.

Safety and tolerability will be monitored during the follow up period of 3 days post last dose (Day 7). Hemodynamic parameters and AEs will be recorded in addition to any agitation episodes that occur during follow up. During follow up period, agitation episodes will be rated pre-dose using the PEC scale but not treated with IGALMI, rather, during the follow up period, subjects will be treated with their standard of care (SOC).

8.2. Study Sites

The study will take place at up to 3 sites in the US.

9. SUBJECT POPULATION

Selection of study population:

9.1. Inclusion Criteria

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

1. Male and female subjects between the ages of 18 to ≤ 65 years.
2. Subjects who have met DSM-5 criteria for schizophrenia, schizoaffective, or schizophreniform disorder or bipolar I or II disorder.
3. Subjects who are judged to be clinically agitated at pre-dose with a total score of ≥ 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the Positive and Negative Syndrome Scale – Excited Component (PEC).
4. Subjects who are currently moderate to severely agitated at least 3 days a week.
5. Subjects who read, understand, and provide written informed consent.
6. Subjects who are in good general health prior to study participation as determined by a detailed medical history and in the opinion of the Principal Investigator.
7. Female subjects, 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.
8. Subjects must be willing to remain in-clinic for the duration of the study.
9. Subjects must have been taking medication for the treatment of schizophrenia or bipolar disorder for at least 30 days prior to screening.

9.2. Exclusion Criteria

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

1. Subjects 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, barbiturates, antihistamines, sedating antidepressants, triptans, opioids, antipsychotics, and antihypertensives in the 4 hours before study treatment.
3. Subjects with congenital prolonged QT syndrome.

4. Prior treatment with IGALMI.
5. Suicidality as assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). A score of ≥4 on the Ideational Component in the last year is exclusionary. Clinically significant risk of suicide based on the Investigator's clinical opinion or a history of an actual suicide attempt in the last year are also exclusionary; or self-injurious behavior that is active.
6. Female subjects who have a positive pregnancy test at baseline or are breastfeeding.
7. Subjects 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.
8. History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1, 3 and 5 min measurements), a pre-dose heart rate of < 55 beats per minutes or systolic blood pressure <110 mmHg or diastolic BP <70 mmHg.
9. Subjects with clinical 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.
10. Subjects 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.
11. Subjects who have received an investigational drug within 30 days prior to the current agitation episode. Subjects who are considered by the investigator, for any reason, to be an unsuitable candidate for receiving dexmedetomidine; e.g., subjects with a history of allergic reactions to dexmedetomidine.

9.3. 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

In this open label, single arm study, all subjects will receive single doses of 180 µg of IGALMI as needed for the treatment of agitation over a period of 7 days.

10.2. Identification of Investigational Product

Commercial foil pouches of IGALMI will be supplied to the sites. IGALMI 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 min.

Individual film appearance is as follows:

- 180µg – Blue 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, subjects 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 subject will self-administer under the supervision of a trained staff member. If the subject 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 90 µg (180 µg film cut in half) after the 2-hour timepoint in the absence of dose-limiting adverse events or safety concerns. A maximum of 2 re-doses will be allowed in a 12-hour period.

10.4. Storage

No special transport or storage conditions are required for IGALMI. Packaged films should be stored at 20°-25°C (68°-77 °F) with excursions permitted between 15°-30°C (59°-86°F).

10.5. Labeling

Commercial labeled180 µg IGALMI pouches will be used for this study, including lot number and expiration date.

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.

If a repeat (90 μg) dose is administered any half unused film must be retained in the original opened pouch, for drug accountability.

10.7. Treatment Compliance

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

10.8. 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.

10.9. 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.

10.9.1. 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.

10.9.2. Prohibited Therapies

The following medications are prohibited within the 4 hours before dosing of study treatment and 2 hours after dosing:

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

If any of the above were used for the indication of insomnia, then that must be clearly recorded in CRF and source documents.

All assessments should be completed prior to any of the medications in section 10.9.2 being taken. If not possible, this should be clearly recorded in source documents.

Subjects should not begin a new treatment regimen for their schizophrenia or bipolar disorder during the conduct of the study.

11. STUDY PROCEDURES

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

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

- Obtain written informed consent
- Review inclusion and exclusion criteria
- Collect demographic information
- Record medical history
- Physical examination including weight, height, body mass index
- ECG
- Neurological examination
- Urine pregnancy test for all females of childbearing potential
- UDS and Breathalyzer
- Safety laboratory assessments
- Vital signs (Resting/Recumbent and Orthostatic)
- Heart rate
- C-SSRS
- Record concomitant medication use (including prior and current therapies (e.g., prescription and non-prescription medications)
- Assess and review AEs

The Screening Visit may be conducted over more than one day; however, all procedures must be completed prior to subject enrolment and within 15 days of first dose.

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

If re-screen occurs greater than 30 days from Screening visit, all Screening assessments must be completed. If less than 30 days, re-screen assessments will be completed on a case-by-case basis with PI and Sponsor discretion.

11.2. Days 1 – 7, Pre-Dose

The following procedures will be performed prior to dosing:

- Review inclusion and exclusion criteria

- Assess and record AEs
- Record concomitant medication use
- Urine pregnancy test for all females of childbearing potential (only at pre-dose Day 1, first agitation episode only).
- UDS and breathalyser (only at pre-dose Day 1, first agitation episode only)
- Vital signs (Resting/Recumbent and Orthostatic) (prior to agitation episodes if possible)
- Heart rate (prior to agitation episodes if possible)
- CGI-S
- PEC (within 15 min of dosing)
- ACES Day (within 15 minutes prior to dosing)
- Trial drug administration

Upon completion of the pre-dose procedures, the subject will be enrolled to study treatment (180µg IGALMI), study drug administration will occur, and the following procedures will be performed 2 hours post-dose (+/- 30 minutes) (Refer to the Schedule of Events, Table 3.1, for specific time points):

11.3. Days 1 – 7, Post-Dose Assessments

- Assess and record AEs
- Record concomitant medication use
- Vital Signs (Resting/Recumbent and Orthostatic)
- Heart rate
- ECG (only Day 1, 2 hours post first dose)
- ACES (2 hours post every dose)
- CGI-I
- PEC

In the event of persistent or recurrent agitation, investigators may choose to repeat dose at 90 µg after the 2-hour time point in the absence of dose-limiting adverse events or safety concerns. A maximum of 2 re-doses will be allowed in a 12-hour period.

11.4. Days 8 – 10, Follow Up/Early Termination

The following procedures will be performed on Days 8 – 10:

- Assess and record AEs
- Record concomitant medication use
- Vital signs (Resting/Recumbent and Orthostatic) (prior to agitation episodes if possible). If no agitation episode occurs resting vital signs and orthostatic vital signs must be collected daily during this period

- Heart rate (prior to agitation episode if possible). If no agitation episode occurs heart rate must be collected daily during this period
- ECG (to be performed during follow up/Early Termination period regardless if subject had an agitation episode. If subject was dosed on Day 7 ECG should be collected at least 24 hours post their last dose on Day 7)
- PEC (before and after dosing with subjects' SOC medication at the time of an agitation episode)

12. STUDY ASSESSMENTS

12.1. Efficacy

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

12.1.1. PANSS – Excitatory Component (PEC)

Assessment of drug effect on acute agitation will be done using the Positive and Negative Syndrome Scale – Excited Component (PEC) according to the Schedule of Events (Table 3.1). The PEC comprises 5 items associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each scored 1 (minimum) to 7 (maximum). The PEC, the sum of these 5 subscales, thus ranges from 5 to 35.

12.1.2. Clinical Global Impressions-Improvement (CGI-I)

Drug response on agitation will be evaluated by the Clinical Global Impressions – Improvement (CGI-I). It will be performed according to the Schedule of Events (Table 3.1). 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

CGI-I will be focused on the severity of agitation rather than the severity of the overall illness of schizophrenia or bipolar disorders.

12.1.3. Clinical Global Impression-Severity (CGI-S)

Clinical Global Impression of Severity (CGI-S) will be rated based upon the severity of agitation at Pre-dose (immediately prior to start of dosing) and performed according to the Schedule of Events (Table 3.1).

Severity of agitation will be assessed based on following scale:

0 = Not assessed

1 = Normal not at all symptomatic

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

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

4 = Severely symptomatic- very marked symptoms make it difficult for subjects to engage with others

12.2. Safety

Safety will be assessed during the study by the monitoring and recording of AEs, vital sign measurements (systolic and diastolic blood pressures, heart rate measured as pulse, respiratory rate, and temperature), ECGs, and ACES scores physical examination findings according to the Schedule of Events (Table 3.1).

12.2.1. Adverse Events

12.2.1.1. 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.

12.2.1.2. 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.

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.

12.2.1.3. 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 MedDRA will be used to code all AEs.

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

The investigator or designee must report any AE that meets the criteria for an SAE (Section 12.2.1.1) to BioXcel's vendor designee within 24 hours of first becoming aware of the event by e-mail or fax using an SAE report form. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Investigator information (name, phone, fax, e-mail)
- Protocol number

- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken

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

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

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

12.2.1.3.1. 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.

12.2.1.3.2. 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.

12.2.1.3.3. 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.

12.2.1.4. Follow-up of Adverse Events

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

12.2.2. 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.

12.2.3. Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at Screening.

Local Labs:

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

12.2.4. 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 of 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

12.2.5. ACES

The Agitation-Calmness Evaluation Scale (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 (Katagiri et al, 2013).

12.2.6. Electrocardiogram

Triplicate (30-60 sec intervals) 10-second (sec) surface 12-lead ECG will be performed at the timepoints specified in the Schedule of Events (Table 3.1). Date and time of ECG, ventricular heart rate (beats/minute), P-R interval, QRS calculated. Normal ranges for ECG parameters will be as per the CRO's current values for these ranges. To determine the presence of QT prolongation, the ECG is to be read, and the site staff will calculate the QTcF values immediately after the ECG has been performed. QTcF prolongation is present if the QTcF value is >450 msec for males and > 470 msec for females or increases≥ 60 msec from Baseline.

12.2.7. Physical Examination

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

12.2.8. Concomitant Medications

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

13. STATISTICAL METHODS

13.1. General Considerations

A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be finalized before database lock.

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

Planned analyses are descriptive in nature and no inferential statistics will be applied.

13.2. Analysis Populations

The following analysis populations are planned:

Enrolled Population: All subjects that complete the pre-dose procedures for first dose and are deemed eligible to receive study treatment (180µg IGALMI).

Safety Population: All Enrolled Population subjects who receive at least one dose of study drug.

Full Analysis Set (FAS) Population: All Enrolled Population subjects who receive at least one dose of study drug and have at least one dose with a pre-dose and post-dose PEC Score, or at least one CGI-I Score, or at least one CGI-S Score after first dose.

13.3. Statistical Analyses

Analyses will be descriptive in nature. All available data will be included in the analyses. Missing data is not anticipated at the 2 hour primary time point.

Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented.

Individual data will be listed by subject and time of assessment. Plots of individual subject values over time will be provided. As appropriate, additional figures may be created to supplement any of the analyses.

Details of the statistical analyses will be provided in the Statistical Analysis Plan which will be finalized prior to database lock.

13.3.1. Subject Disposition and Demographic Characteristics

Subject disposition will include the number of subjects screened and the number and percentage of subjects included in each analysis population. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be presented for the Enrolled Population.

Demographics and baseline characteristics, including age, sex, race, weight, height, and body mass index (BMI), will be summarized for the Enrolled Population.

13.3.2. Tachyphylaxis and Withdrawal Analyses

Tachyphylaxis/Tolerance assessment: Tachyphylaxis/tolerance assessment will be conducted on the FAS Population. PEC scores will be summarized by observed and change from baseline and pre-dose values using descriptive statistics. CGI-I and CGI-S scores will be summarized

using descriptive statistics at post-dose and pre-dose, respectively (note that subjects with CGI-I and CGI-S scores of 0, indicating the assessment was not done or is missing, will be excluded from the summaries of continuous statistics). CGI-S scores at pre-dose will also be summarized by changes from baseline using descriptive statistics.

Number and percentage of PEC and CGI-I responders for each treated episode will be summarized. PEC responders are those with at least a 40% reduction in PEC total score from pre-dose at 2 hours post-dose of study treatment. CGI-I responders are those with a CGI-I score of 1 or 2 at 2 hours post-dose of study treatment.

Withdrawal Assessment: The occurrence of withdrawal in an individual subject in the Safety Population will be described as the occurrence of adverse events including tachycardia, systolic hypertension, nausea, or vomiting and the emergence of any new AEs on ≥2 consecutive days of the 3-day off treatment period.

Data listings for subjects meeting withdrawal criteria will be provided and the number and percentage of subjects meeting withdrawal criteria will be summarized.

13.3.3. Safety Analyses

All safety analyses will be performed using the Safety Population, defined as those subjects receiving at least one dose of study drug.

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 the latest version of the MedDRA. Incidence of AEs will be summarized overall, by severity, and by relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented.

Vital signs, ECG data, and ACES scores will be summarized by observed and change from baseline and/or pre-dose values using descriptive statistics.

For vital sign parameters, low and high values will be defined and summarized as presented in the table below:

	Low	High
Supine HR	≤ 50 beats/min and decrease from pre-dose ≥20 beats/min	≥ 100 beats/min and change from pre-dose ≥ 20 beats/min
Supine SBP	≤ 90 mmHg and decrease from pre-dose ≥20 mmHg	≥ 140 mmHg and change from pre-dose ≥ 20 mmHg
Supine DBP	≤ 50 mmHg and decrease from pre-dose≥10 mmHg	≥ 90 mmHg and change from pre-dose ≥ 10 mmHg
Orthostatic* HR	NA	≥ 30 beats/min
Orthostatic* SBP	Decrease of ≥ 20 mmHg	NA
RR	≤ 11 msec	≥ 17 msec
Orthostatic* DBP	Decrease of ≥ 10 mmHg	NA
*: standing – supine.		
HR = heart rate SBP = systolic blood pressure DBP = diastolic blood pressure RR = respiration rate		

Individual data will be listed by subject and time of assessment.

13.4. Sample Size Determination

There is no hypothesis testing in this study due to its open label nature. The sample size is based on clinical experience and judgment relative to study design and objectives. Given the clinical data available to date for IGALMI, and that the nature of this exploratory study a sample size of at least 20 subjects on active drug should provide adequate clinical information to meet the objectives of the study.

14. STUDY CONDUCT

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

14.1. Sponsor and Investigator Responsibilities

14.1.1. Sponsor Responsibilities

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

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

14.1.2. Investigator Responsibilities

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

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International 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.

14.3.1. Good Clinical Practice Documents

The GCP documents are listed below.

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

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

14.3.2. Case Report Forms

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

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

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

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

14.3.3. Source Documents

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

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

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.

14.4.1. Monitoring Procedures

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

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

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

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

14.4.2. Data Management

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

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

14.4.3. Quality Assurance/Audit

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

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

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

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

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

14.5. Study Termination

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

14.5.1. Regular Study Termination

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

14.5.2. Premature Study Termination

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

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

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

14.6. Study Site Closure

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

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

14.6.1. Record Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study. 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.

14.6.2. Sample Retention

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

14.7. Changes to the Protocol

This protocol cannot be altered or changed except through 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, 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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