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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BioXcel Therapeutics, Inc.

STATISTICAL ANALYSIS PLAN

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
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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
ADaM	Analysis Data Model
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DD	Drug Dictionary
ECG	electrocardiogram
FAS	Full Analysis Set
HR	heart rate
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Affairs
PEC	Positive and Negative Syndrome Scale – Excited Component
PT	preferred term
PRN	as needed
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SOC	system organ class
SBP	systolic blood pressure
TFL	tables, figures, and listings
TEAE	treatment-emergent adverse event
UDS	urine drug screen
WHO-DD	World Health Organization-Drug Dictionary

3 INTRODUCTION

3.1 Preface

This document presents the statistical analysis plan (SAP) for BioXcel Therapeutics, Inc. Study BXCL501-404 (Characterization of Tachyphylaxis, Tolerance, and Withdrawal After

Discontinuation of IGALMI in Frequently Agitated Schizophrenic or Bipolar Patients After 7 Days of PRN Treatment).

Reference materials for this statistical plan include Study Protocol BXCL501-404 Version 6.0 dated 26 October 2023 and Guidance for Industry: E9 Statistical Principles for Clinical Trials (1998).

The SAP described hereafter is an *a priori* plan. Any changes to this SAP will be finalized and approved prior to study database lock. Statistical programming may occur as study data accumulate so that analysis programs are ready at study completion.

3.2 Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess 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. Results from the analyses completed will be included in the final clinical study report for Study BXCL501-404 and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. Exploratory analyses will be clearly identified in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report but will be fully documented in the document containing the additional analyses.

3.3 Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the Study BXCL501-404 protocol except for those items detailed here.

Protocol Section 13.3.3 Safety Analysis includes a table of thresholds for assessing vital signs results, including respiration rate, as low and high. However, this assessment of respiration rate is not of interest and is not included in this SAP.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective of this study is to characterize tachyphylaxis, tolerance and withdrawal after 7 days of PRN treatment with IGALMI for agitation associated with schizophrenia or bipolar disorder.

4.1.2 Secondary Objective

The secondary objective of this study is to determine the safety and tolerability of IGALMI under the studied dosing conditions.

4.2 Study Endpoints

4.2.1 Tachyphylaxis, Tolerance, and Withdrawal Endpoints

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

4.2.2 Safety and Tolerability Endpoints:

Objective	Endpoint
Secondary: To determine the safety and tolerability of IGALMI under the studied dosing conditions	Safety and tolerability endpoints include summaries of the following: • 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)

5 STUDY METHODS

5.1 General 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 the 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 AEs. 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 AEs 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.

5.2 Schedule of Events

Activity	*Screening (Within 15 days of first dose)	Days 1 – 7 PRN Dosing (Per Episode)		Follow Up/Early Termination
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	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 Day 1.

[5] ECG to be performed during follow up/Early Termination period regardless of whether 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.

5.3 Randomization and Blinding

This study is not randomized or blinded. This is an in-clinic, single arm, open label study where subjects will sublingually 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. All subjects will receive single doses of 180 μg of IGALMI as needed for the treatment of agitation over a period of 7 days. 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 AEs or safety concerns. A maximum of 2 re-doses will be allowed in a 12-hour period.

5.4 Analysis Variables

Variables to be analyzed include demographics and baseline characteristics, efficacy variables (changes in PEC scale, PEC responder rates, and CGI-I responder rates), and safety variables (AEs, vital signs, screening lab assessments, 12-lead ECGs, ACES, and physical and neurological exam data).

Derived variables from study endpoints are described within the sections describing the analyses for these endpoints.

6 SAMPLE SIZE

No formal statistical assessment, in terms of sample size, has been conducted. 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.

6.1 Analysis Populations

There will be 3 analysis populations defined for this study.

6.1.1 Enrolled Population

The Enrolled Population will consist of all subjects that complete the pre-dose procedures for first dose and are deemed eligible to receive study treatment (180 μg IGALMI).

6.1.2 Safety Population

The Safety Population will consist of all Enrolled subjects who receive at least one dose of study drug.

6.1.3 Full Analysis Set (FAS) Population

The FAS Population will consist of 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.

6.2 Covariates and Subgroups

6.2.1 Planned Covariates

N/A (no statistical modeling is planned).

6.2.2 Subgroups

N/A (no subgroup analysis is planned).

6.3 Management of Analysis Data

6.3.1 Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data points.

6.3.1.1 Handling of Missing Date Values

Partial or Missing Dates

Partial or missing dates will not be imputed.

6.3.1.2 Imputation Methods

Adverse Events

AEs with missing date information will be considered treatment-emergent if the non-missing portion of the date does not rule that out.

If the relationship of an AE is missing, it will be considered definitely treatment-related for analysis.

Missing AE severity grade will be coded as 3 (severe).

Prior and Concomitant Medication

For determining prior or concomitant status for a medication, in the event that the start or end dates of the medication are unknown or incomplete, the medication will be considered as prior and concomitant unless the non-missing date information, if any, is enough to conclude that the medication could not be prior or, separately, could not be concomitant.

6.3.2 Handling of Early Termination Visit Information

If a subject is terminated early from this study the early termination visit data will be analyzed at the closest scheduled collection time point. If the closest scheduled collection time point has valid data, the early termination data will be assigned to the next scheduled collection time point.

6.3.3 Pooling

Data will be pooled over study sites for analysis.

6.3.4 Coding Conventions for Events and Medications

All AEs and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 26.0 or later) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version March 2023 or later).

6.3.5 Analysis Software

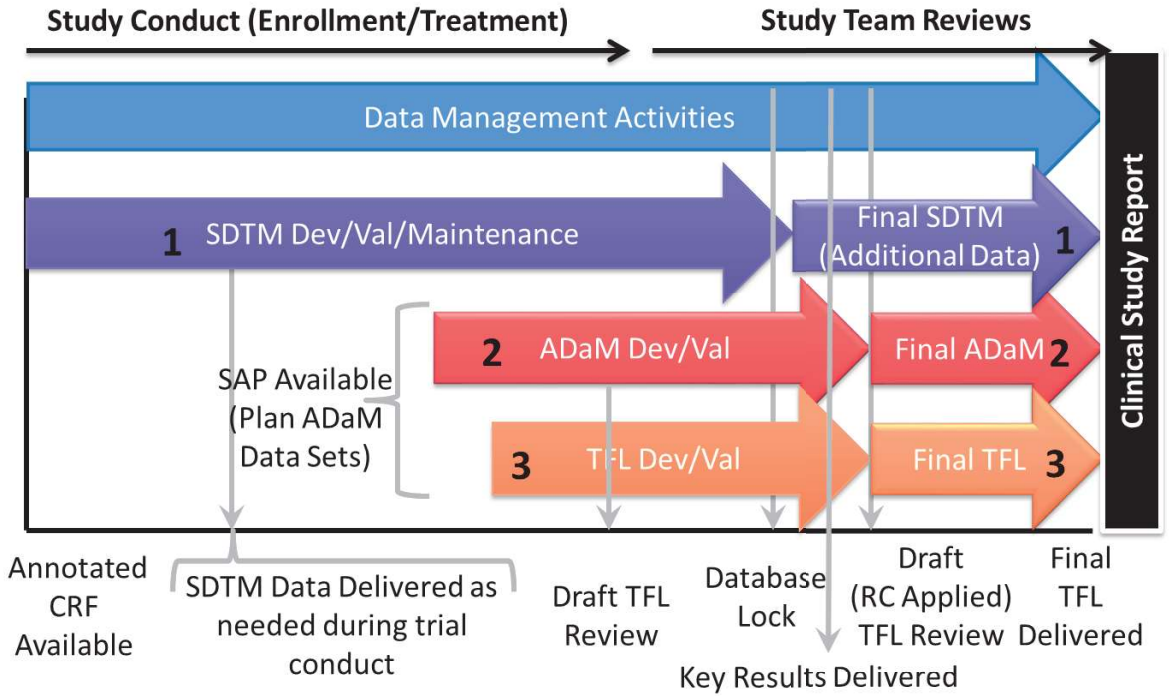
Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics (if they occur, though they are not preplanned in this SAP), and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

6.3.6 Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide v3.3 or later and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM Implementation Guide v1.2 or later) architecture. All planned analyses will be performed using the ADaM data sets developed for this study. Controlled Terminology (31 March 2023 or later) will be used.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 3.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, Validation, and Maintenance of SDTM Domains
2. Development and Validation of ADaMs, with input source the appropriate SDTM domains.
3. Development and Validation of Tables, Figures, and Listings (TFL), with input data source the analysis specific ADaM data sets.

6.4 Planned Study Analyses

6.4.1 Statistical Summaries: Descriptive

Analyses will be descriptive in nature.

Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, 1st quartile, 3rd quartile, minimum, and maximum). For categorical variables, frequencies and percentages will be presented.

All available data will be included in the analyses.

Missing data is not anticipated at the 2-hour primary time point.

Baseline will be the last response prior to first study dose.

Change from baseline scores will be calculated as the post-baseline value minus the baseline value.

Change from pre-dose scores will be calculated as the post-dose value minus the pre-dose value.

Study Day 1 is defined as the study day that the subject has first study dose.

In general, unless otherwise specified, summaries and analyses will be tabulated for all subjects combined.

All study related data collected, and all derived data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

6.4.2 Interim Analyses and Data Monitoring

No interim analysis is planned.

6.5 Statistical Tests

Statistical hypothesis testing is not planned in this SAP. However, if it occurs, it will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. There will be no adjustment for multiplicity. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

7 SUMMARY OF STUDY DATA

7.1 Subject Disposition

A summary will be provided for the following categories: subjects screened, subjects in the Enrolled Population, subjects in the Safety Population, and subjects in the FAS Population. All percentages will be based on the number of subjects in the Enrolled Population.

End of trial information will also be summarized in this table, including the number and percentage of subjects completing the study and the number and percentage of subjects who prematurely discontinued the study with reasons for withdrawal (including AE, lost to follow-up, non-compliance, physician decision, Sponsor decision, pregnancy, site terminated by Sponsor, study terminated by Sponsor, withdrawn consent by subject, and unique “other” reasons captured on the CRF). All percentages will be based on the number of subjects enrolled.

A by-subject data listing of study disposition data, including completion information and reason for study withdrawal will be presented for all enrolled subjects.

7.2 Protocol Deviations

The number of major protocol deviations and number and percentage of subjects with major protocol deviations, by category, will be summarized for the Enrolled Population.

All protocol deviations will be presented in a by-subject data listing for all enrolled subjects.

7.3 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively for continuous and categorical data. Data to be summarized will include sex assigned at birth, age in years, race, ethnicity, height, weight, body mass index (BMI), childbearing potential, smoking and cannabis history, screening laboratory values, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Screening laboratory values include the following:

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)

The demographic data and baseline characteristics will be summarized for the Enrolled Population.

All demographics and baseline characteristics data will be provided in a by-subject listing.

7.4 Medical History

Medical history will be coded using MedDRA, and the number and percentage of subjects will be summarized descriptively for categorical data by system organ class (SOC) and preferred term (PT). Within each preferred term, subjects will be counted only once if they had more than one event reported.

Medical history will be summarized for the Safety Population and for the FAS Population.

Medical history data will be presented in a by-subject listing.

7.5 Prior and Concomitant Medications

The number and percentage of subjects taking concomitant medications will be summarized descriptively for categorical data by Anatomical Therapeutic Chemical (ATC) level 4 and PT. Subjects will only be counted once within each category of medication taken.

The number and percentages of prior medications will be summarized similarly to concomitant medications in a separate table.

Concomitant medication is defined as any medication taken on or after the day of first dose of study drug. A prior medication is defined as any medication that starts and ends prior to the first dose day of study drug.

Prior and concomitant medication data will be summarized for the Safety Population.

Prior and concomitant medication data will be presented in a by-subject listing.

7.6 Treatment Accountability, Compliance and Exposure

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

Treatment exposure will be tabulated and summarized descriptively for continuous data using the Safety Population. Data to be summarized will include the total initial and repeat number of IGALMI doses taken, the total amount of IGALMI in μg taken, and the total number of doses taken using rescue/standard of care (tabulated by Study Days 1-7 and Study Days 8-10 respectively). The number of subjects will be tabulated categorically by the total number of IGALMI doses taken also.

Treatment accountability, administration, and exposure data will be presented in a by-subject listing for the Safety Population.

8 TACHYPHYLAXIS/TOLERANCE/WITHDRAWAL ANALYSES

Tachyphylaxis, tolerance, and withdrawal data will be tabulated and summarized descriptively for continuous and categorical data. Data to be summarized will include observed score, change from baseline, and change from pre-dose, where appropriate, in PEC, CGI-I, CGI-S, and withdrawals.

As subjects can be dosed with IGALMI up to 3 times a day during Days 1 through 7 (first IGALMI dose at 180 μg followed by up to 2 repeat doses at 90 μg within a 12-hour period) and as many times as necessary with their standard of care medication during Days 8 through 10, summaries will be presented by time point. Time points are defined as the study day, dose # within that day, and pre- and post-collection within that dose (Day 1: Pre-Dose 1, Day 1: Post-Dose 1, Day 1: Pre-Dose 2, Day 1: Post-Dose 2, Day 1: Pre-Dose 3, Day 1: Post-Dose 3, Day 2: Pre-Dose 1, Day 2: Post-Dose 1, etc.).

All tachyphylaxis, tolerance, and withdrawal data will be provided in a by-subject listing.

8.1 PEC

Assessment of treatment effect on acute agitation will be done using the PEC, summarized for the FAS Population. The PEC comprises 5 items associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each scored 1 (minimum agitation) to 7 (maximum agitation). The PEC, the sum of these 5 subscales, thus ranges from 5 to 35. The PEC and the 5 individual subscores will be summarized for continuous data by time point. Summaries will be presented for observed score, change from baseline, and change from pre-dose by time point for Days 1 through 10.

Similarly, the PEC and 5 individual subscores will be summarized for continuous data by study dose number: 1st IGALMI dose taken, 2nd IGALMI dose taken, 3rd IGALMI dose taken, etc., irrespective of the study day each dose was taken by each subject. This summary will include observed score and change from pre-dose.

Observed, change from baseline, and change from pre-dose PEC will be presented graphically using spaghetti plots of individual subjects by time point for Days 1 through 10. Similarly observed and change from pre-dose PEC will be presented by IGALMI study dose number.

The count and percentage of subjects defined as PEC responders will be summarized by time point. PEC responders are defined as subjects who have at least a 40% reduction in PEC total score from pre-dose to 2hrs post-dose of study treatment. Percentage change from pre-dose in PEC total score, which has a possible range of 5-35, is calculated as 100 times change from pre-dose divided by (pre-dose minus 5). Response rates will be calculated for each study dose on Days 1 through 10. Response rates will also be calculated by IGALMI study dose number.

Response rate will be presented via bar chart by time points on Days 1 through 10 and by IGALMI study dose number.

Note that PEC scores that do not reach the threshold for dosing will not be summarized but will be included in the by-subject listing.

8.2 CGI-I

Treatment response on improvement in agitation will be evaluated by the CGI-I for the FAS Population. The CGI-I scores range from 0 to 7 (0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse).

Observed CGI-I will be summarized descriptively as continuous and categorical on Days 1 through 7 by post-dose time points and by IGALMI study dose number. Note that scores of 0 will be excluded.

Observed CGI-I will be presented graphically using spaghetti plots of individual subjects by Days 1 through 7 post-dose time points. Note that scores of 0 will be excluded.

The count and percentage of subjects defined as CGI-I responders will be summarized by Days 1 through 7 post-dose time points and by IGALMI study dose number. CGI-I responders are defined as subjects who have a score of 1 or 2 at 2hrs post-dose of study treatment.

Response rate will be presented by bar chart for post-dose time points on Days 1 through 7 and by IGALMI study dose number.

8.3 CGI-S

Treatment response on severity of agitation will be evaluated by the CGI-S for the FAS Population. The CGI-S scores range from 0 to 4 (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).

Observed CGI-S will be summarized descriptively as continuous and categorical on Days 1 through 7 by pre-dose time points and by IGALMI study dose number. Change from Baseline will also be summarized descriptively as continuous. Note that scores of 0 will be excluded from these summaries.

Observed CGI-S will be presented graphically using spaghetti plots of individual subjects by pre-dose time points on Days 1 through 7. Note that scores of 0 will be excluded.

8.4 Withdrawal

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

The count and percentage of subjects who withdraw will be summarized for the Safety Population.

9 SAFETY ANALYSES

All Safety analyses will be conducted using the Safety Population.

Safety data will be tabulated and summarized descriptively for continuous and categorical data. Data to be summarized will include AEs, vital signs, ACES, ECG data, and physical and neurological exam data. Where appropriate, summaries will present observed, change from baseline, and change from pre-dose.

As subjects can be dosed with IGALMI up to 3 times a day during Days 1 through 7 (first IGALMI dose at 180 μg followed by up to 2 repeat doses at 90 μg within a 12-hour period) and as many times as necessary with standard of care medication during Days 8 through 10, where appropriate, summaries will be presented by time point as defined in Section 8 Tachyphylaxis/Tolerance/Withdrawal Analyses.

All safety data will be provided in a by-subject listing.

9.1 Adverse Events

Treatment-Emergent AEs (TEAEs) will be summarized overall and by severity, seriousness, and relationship to treatment, TEAEs leading to discontinuation of study drug, and TEAEs leading to study discontinuation. AEs starting after the administration of first dose of study medication will be considered to be TEAEs

The number and percentage of subjects, as well as frequency of TEAEs, will be summarized descriptively for categorical data and displayed by SOC and PT. At each level of summarization (SOC and PT) subjects are only counted once.

All AE data will be presented in a by-subject listing. A separate listing of serious AEs will also be presented.

9.2 Vital Signs

Resting and Orthostatic vital signs will be collected at screening, pre-dose and 2hrs post-dose, and prior to agitation episodes, if possible. Note that orthostatic vitals are to be collected at 1 minute, 3 minutes, and 5 minutes at each of these scheduled time points.

Resting and orthostatic vital signs include systolic, diastolic blood pressure, and heart rate (measured as pulse). 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 time points.

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

The average of vital signs collected in triplicate will be used in the summary tables. The change from pre-dose to 2 hours post-dose will be calculated for each study dose on Days 1 through 7, and on each standard of care dose for Days 8 through 10. Summaries will present observed, change from baseline, and change from pre-dose by time point.

The difference in resting and orthostatic vital signs for heart rate, systolic blood pressure, and diastolic blood pressure, defined as orthostatic – resting at each pre-dose and post-dose time point, will also be summarized presenting observed, change from pre-dose, and change from baseline. The average of triplicate measurements, where collected, will be used to calculate this difference.

Resting vital signs, orthostatic vital signs, and the difference (orthostatic – resting), observed, change from baseline, and change from pre-dose will be presented graphically using spaghetti plots of individual subjects by time point.

The number and percentage of subjects with low, normal, and high results will be summarized descriptively for categorical data by time point. The tabulation will include Low, Normal, and High categories defined in the Table 1 Vital Signs Low/High Ranges (Normal is defined as a result that is not defined as Low or High):

Table 1 Vital Signs Low/High Ranges

	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
Orthostatic* DBP	Decrease of ≥ 10 mmHg	NA
*: standing – supine.		
HR = heart rate SBP = systolic blood pressure DBP = diastolic blood pressure		

Unscheduled time points will not be summarized.

A by-subject listing of all vital signs data will be presented.

9.3 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. The ACES scores will be collected at pre-dose and 2hrs post-dose on Days 1 through 7 and will be summarized descriptively by time point for observed, change from baseline, and change from pre-dose to 2hrs post-dose.

Observed, change from baseline, and change from pre-dose will be presented graphically using spaghetti plots of individual subjects by time point on Days 1 through 7 and by IGALMI study dose number.

A by-subject listing of all ACES data will be presented.

9.4 12-Lead ECG

Continuous ECG parameter data (heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB interval, and QTcF interval) will be recorded in triplicate. The average of the triplicate readings will be summarized descriptively by time point for observed value and change from baseline (post first dose only on Day 1 and during follow up/Early Termination period regardless of whether subject had an agitation episode, noting that if subject was dosed on Day 7, ECG should be collected at least 24 hours post their last dose on Day 7).

Observed and change from baseline for continuous ECG parameters will be presented graphically using spaghetti plots of individual subjects by study day. The average of triplicate readings will be presented for each individual subject at each time point.

The number and percentage of subjects with ECG normal, abnormal not clinically significant, abnormal clinically significant, and not evaluable will be summarized categorically by time point. Percentages will be based on the number of subjects with a non-missing response at each time point.

A by subject listing of all 12-lead ECG data will be presented.

9.5 Physical and Neurological Examinations

By-subject listings of all physical exam data and neurological exam data will be presented.

9.6 Clinical Laboratory Evaluations

Clinical laboratory data is collected at Screening and will be summarized as described in Section 7.3 Demographics and Baseline Characteristics. This data will also be presented in a by-subject listing.

10 REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

10.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a clinical study report (CSR).
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be presented in color with treatment groups distinguished by different

symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.

- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The International Conference on Harmonisation (ICH) numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g., 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.

10.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Safety Males

>60 years of age) used for analysis in a table or figure.

- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g., number missing, median, quartiles, 5%, 95% intervals) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version 9.4 or higher) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000. Any post-hoc changes to reporting conventions will be identified in the study report but will not necessitate a protocol or SAP amendment.

11 REFERENCES

Guidance for Industry: E9 Statistical Principles for Clinical Trials, September 1998

12 REVISION LOG

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision
V2.0	20 May 2024	P. Shale	7.6 8.1 8.2 8.3 9.3	Language updated to present summaries of total initial and repeat number of IGALMI doses taken, the total number of doses taken using rescue/standard of care (tabulated by Study Days 1-7 and Study Days 8-10 respectively), and the number

				of subjects by total number of IGALMI doses taken. Summaries and figures for PEC and the 5 individual subscores by study dose number added. Equation for calculating PEC Responder percentage change from pre-dose clarified. Summaries and figure for CGI-I by IGALMI study dose number added. Summaries for CGI-S by IGALMI study dose number added. Figure for ACES by IGALMI study dose number added.

*First initial and last name.

**Date of final revision acceptance.

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	21 May 2024 | 12:19
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