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

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STATISTICAL ANALYSIS PLAN

PROTOCOL: BXCL501-103

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

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AMENDMENT HISTORY

Not applicable

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse Event
BMI	Body Mass Index
BP	Blood pressure
CDR	Clinical Dementia Rating Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression-Severity
CMAI	Cohen Mansfield Agitation Inventory
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
HR	Heart rate
hr	hour
ITT	Intent to Treat
kg	kilogram
µg/µcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minutes
mL	milliliter
mm	millimeters
mmHG	millimeters of mercury
MMRM	Mixed model repeated measures

Abbreviation	Definition
MMSE	Mini Mental Status Exam
PANSS/PANSS-EC	Positive and Negative Syndrome Scale/ Positive and Negative Syndrome Scale – Excited Component
PAS	Pittsburgh Agitation Scale
PEC	Positive and Negative Syndrome Scale – Excited Component
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SL	Sublingual
SP	Safety Population
TFLs	Tables, Figures, and Listings
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled “A Phase Ib/II, Multicenter, Randomized, Double Blind, Placebo Controlled, Ascending Dose Finding, Efficacy, Pharmacokinetic and Safety Study of BXCL501 in Agitation Associated with Dementia” (V3 07 December 2019; Administrative Letter #1, 14 January 2020; Protocol Clarification Letter #1, 14 January 2020). All planned pharmacokinetic (PK) analyses will be described in a separate PK and PK/PD analysis plan. Mock shells for Appendix 14 of the Clinical Study Report (CSR) will also be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the finalized SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective is to describe the safety and tolerability of single doses of BXCL501 that may be efficacious in treatment of acute agitation associated with dementia.

3.2 SECONDARY OBJECTIVES

Secondary objectives are as follows:

- Describe the onset and magnitude of calming effects of different doses of BXCL501 on symptoms of acute agitation associated with dementia as measured by the Pittsburgh Agitation Scale (PAS) and PANSS-EC (PEC) as compared to placebo.
- Describe the duration of calming as measured by PEC and ACES.
- Describe the tolerability and safety profile of BXCL501, as determined by adverse events and vital signs versus placebo.
- Describe clinical effects as measured by Clinician Global Impression of Severity of agitation scale (CGI-S) and then improvement (CGI-I) after drug administration.
- Describe the frequency of agitated behaviors using the Cohen Mansfield Agitation Inventory (CMAI).
- Determine the approximate time to disappearance of BXCL501 films in the sublingual space.
- Assess the local tolerability via buccal examination after dosing BXCL501 film.

- Describe the pharmacokinetics and exposure and the potential relationship between PK and PD (measures of safety or efficacy) of dexmedetomidine as delivered by sublingual BXCL501 dosing.

4 STUDY DESIGN

4.1 DURATION OF STUDY

The total duration of the study, excluding Screening, will be approximately seven days (Day 1 through follow-up). The duration of study treatment (BXCL501/placebo) is one day.

4.2 NUMBER OF PARTICIPANTS (STUDY POPULATION)

Each cohort will include 10 subjects (8 BXCL501, 2 placebo) enrolled at up to 3 study sites in the United States. Three cohorts are planned, for a total of 30 subjects (24 BXCL501, 6 placebo).

4.3 DESIGN

This is an adaptive Phase Ib/II trial design. It is a randomized, double-blind, placebo-controlled, multiple ascending dose study assessing efficacy, pharmacokinetics, safety and tolerability of BXCL501 dosing in adult (65 years and older) males and females with acute agitation associated with dementia.

The study will attempt to characterize a safe and tolerable dose range in at least 30 subjects, (4:1 randomization to active: placebo) per dose level, at each of the three dose levels, that results in a calming effect as measured using the Pittsburgh Agitation Scale (PAS). It is possible that the sponsor will opt to expand the number of sites and subjects per dose arm as the study progresses. This adaptive design is beneficial as it yields more extensive safety and tolerability data, increases confidence in efficacy by capturing variability in response and exposure, while providing data that is more generalizable for later phase trials.

Evaluation of three (3) doses of 30 µg, 60 µg and 90 µg are planned, with an option to test different doses based on tolerability and safety. This is an adaptive design as doses selected for testing may be different from these, based upon safety reviews. Doses lower or higher may be chosen to test, and repeated, up to 180µg within each cohort. BXCL501 films may be divided in half if needed to deliver half-dose strengths. Except for the first dose cohort (30µg), each subsequent dose level will be authorized after a safety review of the previous dosing cohort. Dosing may be repeated in the case of persistent or recurrent agitation, if there is no significant improvement (CGI-I of 1 or 2 as ‘very much’ or ‘much improved’) and no safety events evident. Dosing may be repeated up to a total of two repeat doses (at the same randomization group Active:Placebo) for all cohorts except for 90 µg dose which can only be repeated once (total 180 µg) if necessary, at 2 hours post first dose but only after the 2-hour assessments are conducted and only within 12 hours post first dose. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than

90/60 diastolic/systolic) and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of 20 points in either SBP or DBP) or if they are experiencing an AE. Not only does this determine individual response to a single dose but determines if a given subject is responsive to a second dose, and may respond to a greater dose, or could be categorized as a non-responder to BXCL501 despite being exposed to a greater total dose.

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

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

In addition to periodic ongoing safety reviews, after accruing each dose cohort a safety and tolerability review will be done by the BioXcel Therapeutics, Inc. medical monitor, clinical pharmacologist, and the PIs (blinded), who will decide to continue or may stop the study. If dose-limiting safety or intolerability is determined, further dosing of a cohort may be stopped, and escalation discontinued. Further assignment to the same dose will be halted, and escalation will be discontinued for the drug-related adverse events specified in the protocol.

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

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

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

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

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on the final study day or upon early termination. For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be of no clinical significance. Subjects presenting with a clinically significant Urinary Tract Infection (UTI) as determined by clinical laboratory tests will be excluded from the study.

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

The PK plasma samples should be collected per Schedule of Events of the protocol.

4.3.1 *SCHEDULE OF EVENTS AND ASSESSMENTS*

Table 1 presents the schedule of study events and assessments.

Table 1: Schedule of Events

Activity	Pre-Screening[8]	Screening	Pre-Dose	Treatment Evaluation Day 1									Day 2 Follow-Up (+1)	Day 3 Discharge	Day 7 (+2)
Time point	Pre-treatment	Pre-treatment	-1 hr to time 0	5 min	10 min	15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	24 hr (-9/+12 hr)		End of Study
Informed Consent	X														
Medical History	X	X													
Demographics	X	X													
Weight	X												X		
Height	X														
Mini-Mental State exam	X												X		
Clinical Dementia Rating Score	X												X		
Physical Exam	X	X											X		
Safety Labs[3]	X													X	X
UTI and pregnancy		X													
ECG with rhythm strip [7]	X		X						X				X		
Pulse oximetry			X				X	X	X	X	X	X	X		
Resting vital signs[2]	X	X	X				X	X	X	X	X	X	X		
Orthostatic vital signs[2]	X	X	X				X	X	X	X		X	X		
Inclusion/Exclusion criteria	X	X	X												
Randomization			X												
CMAI		X	X						X						X
Study drug administration[6]			X												
PAS	X	X	X				X	X	X	X		X	X	X	X
PEC	X		X				X	X	X	X		X	X	X	X
ACES			X					X	X	X		X			
CGI-Severity Agitation			X						X				X		
CGI-Improvement/Change in Agitation							X	X	X	X		X			

C-SSRS	X	X											X		
Buccal (SL) assessment [5]				X	X	X	X		X	X			X		
PK Sampling[4]							X	X	X*	X		X	X		
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CCI [redacted]

4.4 TREATMENT

Evaluation of three (3) doses of BXCL501 30 µg, 60 µg and 90 µg are planned, with an option to test different doses based on tolerability and safety. This is an adaptive design as doses selected for testing may be different from these, based upon safety reviews. Doses lower or higher may be chosen to test, and repeated, up to 180 µg within each cohort.

Dosing may be repeated in the case of persistent or recurrent agitation, if there is no significant improvement (CGI-I of 1 or 2 as 'very much' or 'much improved') and no safety events evident. Dosing may be repeated up to a total of two repeat doses (at the same randomization group Active:Placebo) for all cohorts except for 90 µg dose which can only be repeated once (total 180 µg) if necessary, at 2 hours post first dose but only after the 2-hour assessments are conducted and only within 12 hours post first dose. Patients can only be re-dosed if they are hemodynamically stable, not hypotensive (must be greater than 90/60 diastolic/systolic) and not bradycardic (must be greater than 60 bpm). Patients also cannot be re-dosed if they are orthostatic (a drop of 20 points in either SBP or DBP) or if they are experiencing an AE.

4.5 RANDOMIZATION

Upon confirmation of eligibility, subjects will be randomized to BXCL501 or placebo film. In each of the three-dose cohorts, 10 participants (8 drug treated, 2 placebo) will be randomized 4:1 BXCL501 film: Placebo. Study randomization will be computer generated.

5 OUTCOME VARIABLE DEFINITIONS

5.1 PRE-SCREENING, SCREENING, AND BASELINE CHARACTERISTICS

Pre-Screening: Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight and body mass index (BMI), medical history, prior and concomitant medications, physical examination, resting and orthostatic vital signs, 12-lead electrocardiogram (ECG), clinical laboratory results, urine drug screen, Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR), PAS, PEC, Columbia-Suicide Severity Rating Scale (C-SSRS), and any adverse events will be collected at pre-screening.

Screening: Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight and body mass index (BMI), medical history, prior and concomitant medications, physical examination, resting and orthostatic vital signs, UTI screening, pregnancy test, PAS, C-SSRS, and any adverse events will be collected at screening.

Baseline (Pre-Dose): Inclusion/exclusion criteria, resting and orthostatic vital signs, 12-lead ECG, concomitant medications, CMAI, PAS, PEC, ACES, CGI-S, and adverse events will be collected prior to dose administration.

5.2 EFFICACY ASSESSMENTS

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

5.2.1 *PANSS-EXCITED COMPONENT (PEC)*

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

5.2.2 *COHEN MANSFIELD AGITATION INVENTORY (CMAI)*

Assessment of drug effect on frequency of acute agitation will be also done using the CMAI. The CMAI is a rating questionnaire consisting of 29 behaviors each rated on a 7-point scale of frequency. It is possible that all 29 behaviors will not be relevant to a specific patient.

The CMAI Instruction Manual (Cohen-Mansfield, 1989) acknowledges that the CMAI contains a diversified group of behaviors. The authors propose that researchers conduct their own factor analysis because factors depend on the population studied, and researchers need to conceptualize their understanding of these behaviors in order to aggregate the behaviors in a meaningful way. For these reasons, analysis of factors will be conducted after a determination of the appropriate items to include in each factor, based on the observed data from the study. Factors will most likely include physically aggressive behaviors, physically nonaggressive behaviors, verbally aggressive behaviors, and verbally nonaggressive behaviors.

5.2.3 *AGITATION-CALMNESS EVALUATION SCALE (ACES)*

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

5.2.4 *PITTSBURG AGITATION SCALE (PAS)*

The Pittsburg Agitation Scale (PAS) is an instrument based on direct observations of the patient that is developed to monitor the severity of agitation associated with dementia. There are four Behavior Groups observed (using a 0 to 4-point scale) in the patient, Aberrant Vocalization, Motor Agitation, Aggressiveness, Resting Care.

5.2.5 *CGI-S AND CGI-I FOR AGITATION*

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

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

Severity of agitation will be assessed based on following scale:

0 = Not assessed

1 = Normal not at all symptomatic

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

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

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

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

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

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

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

The CGI-I scores range from 1 to 7:

0=not assessed (missing),

1=very much improved,

2=much improved,

3=minimally improved,

4=no change,

5=minimally worse,

6=much worse,

7=very much worse

5.3 SAFETY AND TOLERABILITY ASSESSMENTS

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate measured

as pulse, respiratory rate, and temperature), ECG, and physical examination findings.

5.3.1 *ADVERSE EVENTS*

An adverse event (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.

5.3.2 *COLUMBIA SUICIDE SEVERITY RATING SCALE*

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

5.3.3 *LABORATORY SAFETY ASSESSMENTS*

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Table 1).

Hematology:	Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serum chemistry:	Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose, albumin, and total protein
Urinalysis:	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test:	Conducted by local labs
Urine Drug Screen:	Cocaine, amphetamine, phencyclidine, benzodiazepines, marijuana. (Note: Marijuana positive is allowed provided subject is not moderately to severely dependent, benzodiazepine positive are allowed if prescribed)

5.3.4 *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. Measurements should be made at least 1 minute apart using the same arm at each visit.

At indicated time points orthostatic measurement of systolic, diastolic blood pressure and heart rate will be measured after the subject has been standing for a total of 5 minutes. Temperature and respiratory rate will be recorded when orthostatic measurement is indicated in the schedule of events and are not required to be measured at resting vital sign 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

5.3.5 *ELECTROCARDIOGRAM*

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

5.3.6 *PHYSICAL EXAMINATION*

A standard physical examination will be performed at Pre-Screening, Screening and 24 hours post dose. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at Screening and weight will be measured again at the Day 2 follow-up visit.

5.3.7 *BUCCAL ASSESSMENTS*

Buccal (SL) exam for local irritation and time to disappearance of the film will be performed by unblinded staff at 5, 10, 15, 30 min, 2 hr, 4 hr and 24 hr post first dose.

5.4 CLINICAL DIAGNOSIS AND DESCRIPTION OF DEMENTIA

The subtype of dementia will be determined and recorded based upon clinical neurologic and psychiatric evaluation to include review of all available medical information, medical records, documentation of prior evaluations, family/caretaker interviews, records, laboratory, genetics or other biomarkers, and results of neuroimaging (if available).

The following scales will characterize subject's dementia (*DSM-5* Major Neurocognitive disorder) in terms of cognitive and functional impairment. Both assessments will occur at the Pre-Screening and Day 2/Follow-Up visits.

5.4.1 *MMSE*

The Folstein Mini-Mental State Examination (MMSE) is an exam that tests an elderly person's cognitive ability. Domains measured by the MMSE include orientation to time and place, registration, attention and calculation, recall, naming, repetition, comprehension, reading, writing, and drawing. Total points on this test is 30. Any score of 24 or more (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.

5.4.2 *CDR*

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

CDR-0 = normal

CDR-0.5 = very mild dementia

CDR-1 = mild

CDR-2 = moderate

CDR-3 = severe

5.5 PHARMACOKINETICS

For each subject, up to 6 blood samples (24 mL of blood) will be collected during the study for PK analysis. Blood samples (4 ml) will be collected at 0.5, 1, 2, 4, 8, and 24 hours post-dose per Table 1 Schedule of Events. A sample may not be collected if the physician in charge of the patient indicates in the source documents that the patient is in a mental state that is not conducive to PK sample collection and record the PEC score at the time of proposed sample collection.

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

5.6 CONCOMITANT MEDICATIONS

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

6 STUDY ENDPOINTS

6.1 PRIMARY ENDPOINTS

6.1.1 *PRIMARY EFFICACY ENDPOINT*

- Change in PEC total score from baseline

6.1.2 *PRIMARY EFFICACY TIME POINT*

- 2 hours post-dose

6.1.3 *PRIMARY SAFETY AND TOLERABILITY ENDPOINTS*

- Comparison of cardiovascular parameters (BP, HR, pulse oximetry, ECG) between BXCL501 30 µg, 60 µg, and 90 µg and placebo

6.2 SECONDARY ENDPOINTS

6.2.1 *SECONDARY EFFICACY ENDPOINTS*

- Change in PEC total score from baseline at 30 min, 1 hr, 4 hr, and 8 hr post-dose, and at Day 2, Day 3, and Day 7
- Percentages of subjects at each dose who achieve a 40% reduction from baseline in PEC total score at 2 hr post-dose ("Responders")
- Change in PAS total score from baseline at 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose, and at Day 2, Day 3, and Day 7
- Change in ACES score from baseline at 1 hr, 2 hr, 4 hr, and 8 hr post-dose
- Change in CGI-S agitation score from baseline at 2 hr post-dose and at Day 2
- CGI-I agitation score at 30 min, 1 hr, 2 hr 4 hr, and 8 hr post-dose
- Change in CMAI total score from baseline at 2 hr post-dose and Day 7

6.2.2 *SECONDARY SAFETY AND TOLERABILITY ENDPOINTS*

- Time taken for medication to dissolve (1-30 sec, 31-59 sec, 1-2 min, 3+ min) – only assessed at 30 minutes
- Negative reaction to the sublingual film in the examiner's opinion (Yes/No) – assessed at 30 min, 2 hr, 4 hr, and 24 hr post-dose

6.2.3 *SECONDARY PHARMACOKINETIC ENDPOINTS*

A separate SAP for the PK analyses will be prepared for the study and will be finalized prior to database lock.

6.3 EXPLORATORY ENDPOINTS

- CCI [redacted]

7 STATISTICAL ANALYSES

Statistical analyses will be performed using SAS® software version 9.4.

7.1 STATISTICAL METHODOLOGY

7.1.1 *SAMPLE SIZE DETERMINATION*

[redacted]
CCI
[redacted]

7.1.2 *POPULATIONS FOR STATISTICAL ANALYSIS*

The following are analysis populations for the study:

- Safety Population: All subjects who receive study drug
- Intent to treat (ITT) Population: All subjects in the Safety Population who have a baseline and at least one post-baseline efficacy assessment
- Per Protocol (PP) Population: All subjects in the ITT Population with no major protocol deviations. PP analyses may not be conducted if there are not sufficient protocol deviations deemed to impact analysis

7.1.3 *STATISTICAL ANALYSES – GENERAL CONSIDERATIONS*

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). The same number of decimal places as in the raw data will be presented when reporting minimum and maximum. One more decimal place than in the raw data will be presented when reporting mean and standard deviation.

For categorical variables, frequencies and percentages will be presented by treatment.

Baseline is defined as the last non-missing observation prior to initiation of study medication.

All statistical testing will be based on a two-sided significance level of 0.05 unless otherwise stated.

Listings for Appendix 16.2 in the CSR will include all the subject data points being collected or derived for analyses. Data listings will be provided for all subjects up to the point of withdrawal.

7.1.4 *PROCEDURES FOR HANDLING MISSING DATA*

No imputation will be performed for missing data unless stated otherwise.

For longitudinal analyses of continuous data, the Mixed Model Repeated Measures is considered valid under a Missing at Random (MAR) missingness mechanism.

7.1.5 *INTERIM ANALYSES*

Due to an unanticipated delay in enrollment and study pause associated with the COVID-19 pandemic, we are planning on conducting a unblinded analysis to gain further experience with the endpoints under consideration and for decision making, including with respect to this study. The following data are planned to be included:

Efficacy:

T14.2.1.1_I	Change from Baseline in PEC Score	ITT
T14.2.2.1_I	Change from Baseline in PAS Score	ITT
T14.2.2.2_I	Change from Baseline in ACES Score	ITT
T14.2.2.3_I	Change from Baseline in CMAI Score	ITT
T14.2.2.4_I	Change from Baseline in CGI-S Agitation Score	ITT
T14.2.3.1_I	Change from Baseline in CMAI Factor Scores	ITT

Safety:

L16.2.8_I	Adverse Events	SP
L16.2.10_I	Vital Signs	SP
L16.2.11.1_I	Electrocardiogram Results	SP
L16.2.12_I	Pulse Oximetry	SP

The intention of the safety analyses is primarily to evaluate the safety data collected in this elderly population. It is likely that this elderly frail population maybe more susceptible to the cardiovascular effects of BXCL501. The evaluation of these safety data will help us to plan the appropriate doses and or cohorts for this study population. In addition, many of the tools employed in this study to assess the effects of BXCL501 on agitation in this population, though widely used in chronic, longer studies, are yet to be fully characterized in a shortened study of this nature. Data from these tools will guide us to the appropriate use of these instruments as we move forward and enable us to choose the most relevant assessments in this study context

7.2 SCREENING AND BASELINE CHARACTERISTICS

Summary tables will be constructed by treatment for the Safety Population for the following Pre-Screening, Screening or Pre-Dose data: demographic characteristics of age, sex, race, ethnicity, weight, height and body mass index (BMI) (Table 14.1.3 in Appendix 14 of the CSR), medical history (Table 14.1.4),

prior medications (Table 14.1.5.1), laboratory examinations (Tables 14.3.5.1-14.3.5.3), vital signs (Table 14.3.6), and ECG (Tables 14.3.7.1-14.3.7.2).

Listings will be provided for eligibility criteria violations, demographics, and medical history (Listings 16.2.2-16.2.4).

7.3 SUBJECT DISPOSITION

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment (Table 14.1.1). The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment (Table 14.1.2). Subject-level listings will be provided (Listings 16.2.1.1-16.2.1.2).

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR.

7.4 STUDY TREATMENT ADMINISTRATION

Study drug administration data will be listed by subject (Listing 16.2.5.2).

7.5 EFFICACY ANALYSES

The efficacy analyses described in this section compare each dose group to the pooled placebo group. Nominal significance levels will be reported with no adjustment for multiple tests.

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

7.5.1 *PRIMARY EFFICACY ANALYSIS*

The primary efficacy endpoint is change from baseline in PEC total score. The primary efficacy time point will be at 2 hr post-dose.

Placebo subjects will be pooled and contrasted with each dose.

A mixed model for repeated measures (MMRM) will be used to assess treatment group differences for change from baseline. Change from baseline scores will include all available time points in a single model; the 2 hr time point is considered primary, and all other time points are considered secondary. Fixed effects will include treatment group, analysis visit, treatment-by-visit interaction, and a baseline-by-visit interaction. Visit will be fit as a repeated effect in the model using the repeated statement in SAS. The baseline score will be included as a continuous covariate. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a Toeplitz structure will be used.

Least squares (LS) means will be presented for treatment and treatment*visit, with the significance level of the treatment-by-visit interaction presented in summary tables. Pair-wise comparisons of differences in LS means, two-sided 95% confidence intervals (CIs) on differences, and p-values will be provided for each active treatment versus placebo for each visit and for treatment main effects (Tables 14.2.1.1-14.2.1.2, ITT and PP populations). Line graphs will be provided reflecting changes from baseline over time (Figures 14.2.1.1-14.2.1.2, ITT and PP populations).

Individual patient scores for the PEC for all time points will be provided in a listing (Listing 16.2.6.1).

7.5.2 *SECONDARY EFFICACY ANALYSES*

All efficacy assessments will be summarized at all available time points over the course of the study. Secondary endpoint comparisons against baseline for all PEC time points will be included in the MMRM for the primary analysis, as described above. Findings from pairwise LS means will be used to differentiate primary versus secondary endpoints. Changes from baseline for PAS, ACES, CGI-S agitation score, and CMAI total score for all available time points will be analyzed using MMRM, using the specifications described above (Tables 14.2.2.1-14.2.2.4). CGI-I agitation score will be compared between treatment and placebo groups using MMRM, however as there is no baseline measurement, it will not be included in the model (Table 14.2.2.5). Listings will be provided for individual patient scores (Listings 16.2.6.2-16.2.6.5). Line graphs will be provided reflecting changes from baseline over time in PAS score (Figures 14.2.2.1.1-14.2.2.1.2, ITT and PP populations).

Responder (ie, percentage change from baseline in the PEC score at 2 hours >40%) comparisons will be made via Fisher's Exact test. Nominal p-values and the treatment difference and associated two-sided 95% confidence interval will be based on the Wald method with continuity correction and reported for each pairwise comparison of BXCL501 and placebo (Table 14.2.2.6). A bar chart will be provided reflecting percentages of responders at each time point for the 3 treatment groups and placebo (Figures 14.2.2.1.2-14.2.2.1.2).

For the CGI-S and CGI-I, scores of 0 (not assessed) will be set to missing prior to analysis.

7.5.3 *EXPLORATORY EFFICACY ANALYSES*

[redacted]
CCI
[redacted]

7.6 SAFETY ANALYSES

All safety analyses will be based on the Safety Population. Safety and tolerability will be assessed by clinical review of all safety parameters including AEs, laboratory values and vital signs. The safety analyses will include all results collected from randomization through the end of the study.

7.6.1 *PRIMARY SAFETY ANALYSES*

Comparison of cardiovascular parameters (BP, HR) between BXCL501 30 µg, 60 µg, and 90 µg and placebo (Table 14.3.1).

7.6.2 *SECONDARY SAFETY ANALYSES*

A frequency summary will be presented for time taken for medication to dissolve at 30 minutes (1-30 seconds, 31-59 seconds, 1-2 minutes, 3+ minutes) and for negative reaction to sublingual film (Yes/No) assessed at 30 min, 2 hr, 4 hr, and 24 hr post-dose. These parameters will be presented for each treatment group at each time point (Tables 14.3.2.1-14.3.2.2). Listings will include subject-level findings as well as all physical findings noted during buccal examinations (Listings 16.2.7.1-16.2.7.2).

7.6.3 *ADVERSE EVENTS*

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 22.0) coding system and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

New conditions detected or diagnosed after study intervention administration meet the definition of an AE even though they may have been present before the start of the study.

The number and percentage of patients who report AEs will be summarized by system organ class and preferred term. Adverse events will also be summarized by severity as well as relationship to Study Medication. For summaries by relationship, relationship will be categorized as related (unlikely, possibly, probably, and definitely related) or not related.

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to Study Medication when summarized by relationship. If a patient reports multiple preferred terms for a system organ class, the patient will be counted only once for that system organ class.

Proportions for adverse events that are gender-specific (e.g., dysmenorrhea) will be based on the number of patients from that gender.

The number and percentage of patients who experience AEs will be summarized by treatment group for the following:

- By system organ class and preferred term (Table 14.3.3.1)
- By severity, system organ class, and preferred term (Table 14.3.3.2)
- By relationship to Study Medication (related, not related), system organ class, and preferred term (Table 14.3.3.3)
- Serious adverse events by system organ class and preferred term (Table 14.3.3.4)
- Serious adverse events by relationship to Study Medication, system organ class, and preferred term (Table 14.3.3.5)
- Adverse events resulting in discontinuation of Study Medication by system organ class and preferred term (Table 14.3.3.6)

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment (Listing 16.2.8).

7.6.4 *COLUMBIA SUICIDE SEVERITY RATING SCALE*

The C-SSRS data will be summarized descriptively. Individual patient data will be provided in a listing (Listing 16.2.16). Only the following specific suicidal ideation and behavior category questions with any “Yes” responses will be summarized in a frequency distribution table at each post-randomization visit (Table 14.3.4):

- Any Suicidal Ideation Category:
    - Wish to be Dead
    - Non-Specific Active Suicidal Thoughts
    - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
    - Active Suicidal Ideation with Specific Plan and Intent
- Any Suicidal Behavior Category:
    - Completed Suicide
    - Non-Fatal Suicide Attempt
    - Interrupted Attempt
    - Aborted Attempt
    - Preparatory Acts or Behavior

- Any Suicidal Ideation or Behavior Category

7.6.5 *CLINICAL LABORATORY EVALUATIONS*

Each laboratory value and change from baseline (when appropriate) will be summarized for hematology, blood chemistry and urinalysis for each treatment and all available time points (Tables 14.3.5.1-14.3.5.3). Individual patient listings will be provided (Listing 16.2.9).

7.6.6 *PULSE OXIMETRY*

A listing of findings from pulse oximetry will be provided by subject (Listing 16.2.12).

7.6.7 *PHYSICAL EXAMINATION*

A listing of abnormal physical examination findings will be provided by subject (Listing 16.2.13). Pregnancy, alcohol screening, and drug testing results will be provided by patient (Listing 16.2.14).

7.6.8 *CLINICAL DIAGNOSIS AND DESCRIPTION OF DEMENTIA*

MMSE and CDR scores will be listed by patient (Listings 16.2.15.1-16.2.15.2).

7.6.9 *VITAL SIGNS*

Vital signs will be summarized at each time point for each treatment group, using descriptive statistics. For any vital signs measured in triplicate, only the 2nd measurement will be included in the descriptive statistics. Change from baseline in vital signs values will also be summarized (Table 14.3.6). Individual patient listings will be provided (Listing 16.2.10).

Baseline will be defined as the last vital sign value obtained before the first dose of Study Medication on Day 1.

7.6.10 *12-LEAD ELECTROCARDIOGRAM*

The change from baseline in ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

Frequency distributions of the QTcF interval will be displayed by treatment group for abnormally high values that are greater than their baseline value at any post-baseline visit and the following data cuts:

>450 msec and > Baseline value

>470 msec and > Baseline value

>500 msec and > Baseline value

Additionally, the change from baseline frequency distributions of the QTcF interval will displayed by treatment group for the following data cuts:

>30 msec increase

>60 msec increase

(Tables 14.3.7.1-14.3.7.2 and Listings 16.2.11.1-16.2.11.2)

7.6.11 *CONCOMITANT MEDICATIONS*

Concomitant medications will be summarized (n and %) by ATC class and preferred term (coded by WHO Drug coding dictionary March 2019) for each treatment group (Table 14.1.5.2). Concomitant medications for individual patients will be provided in a listing (Listing 16.2.5.1).

7.6.12 *STUDY MEDICATION COMPLIANCE*

Study Medication compliance will be measured by the number of days of Study Medication administered and the percentage of scheduled doses that were taken. Descriptive statistics will be used to summarize dosing compliance within each treatment group (Table 14.1.6), as well as provided in a listing per patient (Listing 16.2.5.3). The number and percentage of subjects who have been re-dosed for each treatment group, as well as the number of times each subject was re-dosed, will be summarized using descriptive statistics (Table 14.1.6). A listing of subjects who have been re-dosed, the number of times each subject was re-dosed, and the times of re-dose will be provided (Listing 16.2.5.3).

7.7 PHARMACOKINETIC and PHARMACODYNAMIC ANALYSIS

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

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

limited to, minor deviations between the actual and scheduled time of sample collection.

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

Other PK analyses may be performed as appropriate.

Pharmacodynamic data, including changes in blood pressure & heart rate, and changes in measures of agitation, from baseline may be evaluated as a function of time and as a function of measured or estimated plasma concentrations. Details will be described in the SAP for PK and PK/PD analyses.

8 REFERENCES

Cohen-Mansfield J, Marx MS, & Rosenthal AS. (1989). A description of agitation in a nursing home. *Journal of Gerontology: Medical Sciences*, 44(3), M77-M84.

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

9 TABLES, LISTINGS AND FIGURES

9.1 TABLES

The following tables are to be included in Appendix 14 of the CSR and may be modified with Sponsor's approval.

Table	Title	Population
T14.1.1	Analysis Populations	
T14.1.2	Subject Disposition	SP
T14.1.3	Demographics	SP
T14.1.4	Medical History	SP
T14.1.5.1	Prior Medication	SP
T14.1.5.2	Concomitant Medication	SP
T14.1.6	Re-Dosed Subjects	SP
T14.2.1.1	Change from Baseline in PEC Score	ITT
T14.2.1.2	Change from Baseline in PEC Score	PP
T14.2.2.1	Change from Baseline in PAS Score	ITT
T14.2.2.2	Change from Baseline in ACES Score	ITT
T14.2.2.3	Change from Baseline in CMAI Total Score	ITT
T14.2.2.4	Change from Baseline in CGI-S Agitation Score	ITT
T14.2.2.5	Differences in CGI-I Agitation Scores	ITT
T14.2.2.6	Percentages of Responders in the PEC Score	ITT
T14.2.3.1	CCI [redacted]	ITT
T14.2.3.2	Differences in CMAI Factor Scores	ITT
T14.3.1	Differences in Cardiovascular Parameters	SP
T14.3.2.1	Differences in Time for Medication to Dissolve	SP
T14.3.2.2	Differences in Buccal Assessment Findings	SP
T14.3.3.1	Adverse Events by System Organ Class and Preferred Term	SP
T14.3.3.2	Adverse Events by Severity, System Organ Class, and Preferred Term	SP
T14.3.3.3	Adverse Events by Relationship to Study Medication, System Organ Class, and Preferred Term	SP
T14.3.3.4	Serious Adverse Events by System Organ Class and Preferred Term	SP
T14.3.3.5	Serious Adverse Events by Relationship to Study Medication, System Organ Class, and Preferred Term	SP
T14.3.3.6	Adverse Events Leading to Discontinuation	SP
T14.3.4	C-SSRS Suicidal Ideation or Behavior "Yes" Responses	SP
T14.3.5.1	Summary of Hematology Measurements	SP
T14.3.5.2	Summary of Serum Chemistry Measurements	SP
T14.3.5.3	Summary of Urinalysis Measurements	SP

Table	Title	Population
T14.3.6	Summary of Vital Sign Measurements	SP
T14.3.7.1	Changes in Electrocardiogram Measurements	SP
T14.3.7.2	Frequency of Overall Electrocardiogram Results	SP

9.2 LISTINGS

The following listings are to be included in the post-text Appendix 16 of the CSR and may be modified with Sponsor's approval.

Listing	Title	Population
L16.2.1.1	Subject Disposition	
L16.2.1.2	Analysis Populations	
L16.2.2	Inclusion Criteria Not Met or Exclusion Criteria Met	SP
L16.2.3	Demographics and Baseline Characteristics	SP
L16.2.4	Medical History	SP
L16.2.5.1	Concomitant Medications	SP
L16.2.5.2	Study Drug Administration	SP
L16.2.5.3	Re-Dosed Subjects	SP
L16.2.6.1	PEC Assessment	ITT
L16.2.6.2	PAS Assessment	ITT
L16.2.6.3	ACES Assessment	ITT
L16.2.6.4	CMAI Assessment	ITT
L16.2.6.5	CGI-S and CGI-I Assessments	ITT
L16.2.7.1	Time Taken for Medication to Dissolve	SP
L16.2.7.2	Buccal Assessment for Local Irritation	SP
L16.2.8	Adverse Events	SP
L16.2.9	Clinical Laboratory Results	SP
L16.2.10	Vital Signs	SP
L16.2.11.1	Electrocardiogram Results	SP
L16.2.11.2	Electrocardiogram Findings	SP
L16.2.12	Pulse Oximetry	SP
L16.2.13	Physical Examinations (Abnormal Findings)	SP
L16.2.14	Drug and Pregnancy Screening Results	SP
L16.2.15.1	MMSE Results	SP
L16.2.15.2	CDR Results	SP
L16.2.16	C-SSRS Results	SP

9.3 FIGURES

The following figures are to be included in Appendix 14 of the CSR and may be modified with Sponsor's approval.

F14.2.1.1	Change from Baseline in PEC Score	ITT
F14.2.1.2	Change from Baseline in PEC Score	PP
F14.2.2.1.1	Change from Baseline in PAS Score	ITT
F14.2.2.1.2	Change from Baseline in PAS Score	PP
F14.2.2.2.1	Percentages of Responders in the PEC Score	ITT
F14.2.2.2.2	Percentages of Responders in the PEC Score	PP

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

NCT04251910

04/14/2021

STATISTICAL ANALYSIS PLAN: PART B

PROTOCOL: BXCL501-103

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

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DATE: 14 April 2021

STATUS: Final Version 1.0

Statistical Analysis Plan: Part B
Protocol: BXCL501-103
Final Version: 1.0 Date: 14 April 2021

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TABLE OF CONTENTS

AMENDMENT HISTORY

Not applicable

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse Event
BMI	Body Mass Index
BP	Blood pressure
CDR	Clinical Dementia Rating Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression-Severity
CMAI	Cohen Mansfield Agitation Inventory
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
HR	Heart rate
hr	hour
ITT	Intent to Treat
kg	kilogram
µg/µcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minutes
mL	milliliter
mm	millimeters
mmHG	millimeters of mercury

Abbreviation	Definition
MMRM	Mixed model repeated measures
MMSE	Mini Mental Status Exam
PANSS/PANSS-EC	Positive and Negative Syndrome Scale/ Positive and Negative Syndrome Scale – Excited Component
PAS	Pittsburgh Agitation Scale
PEC	Positive and Negative Syndrome Scale – Excited Component
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SL	Sublingual
SP	Safety Population
TFLs	Tables, Figures, and Listings
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for Part B of the study entitled “A Phase Ib/II, Multicenter, Randomized, Double Blind, Placebo Controlled, Ascending Dose Finding, Efficacy, Pharmacokinetic and Safety Study of BXCL501 in Agitation Associated with Dementia” (V7, 04 February 2021). All planned PK analyses will be specified in a separate document. Mock shells for Appendix 14 of the Clinical Study Report (CSR) will also be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the finalized SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

3 STUDY OBJECTIVES

The objective of Part B is to test a dose of 40 µg as potentially the lowest safe dose that remains effective vs. placebo in reducing agitation. In addition, the data collected in Part B will be from a larger number of sites and raters which enables a more accurate estimate of variance for powering future Phase 3 development studies.

3.1 PRIMARY OBJECTIVE

Describe the safety and tolerability of 40 µg of BXCL501 for study of efficacy in treatment of acute agitation associated with dementia.

3.2 SECONDARY OBJECTIVES

Secondary objectives are as follows:

- Describe the onset and magnitude of calming effects of 40 µg of BXCL501 on symptoms of acute agitation associated with dementia compared to placebo.
- Describe the duration of calming as measured by the Positive and Negative Syndrome Scale Excited Component (PEC) and the Agitation-Calmness Evaluation Scale (ACES).
- Describe the tolerability and safety profile of 40 µg of BXCL501, as determined by adverse events (AEs) and vital signs vs. placebo.
- Describe clinical effects as measured by the Clinician Global Impression of Severity scale (CGI-S) to assess agitation and then Improvement (CGI-I) after drug administration.
- Describe the frequency of agitation using the Cohen Mansfield Agitation Inventory (CMAI) at baseline and 2 hours post-dose.

- Determine the approximate dissolution time of BXCL501 films in the sublingual space.
- Assess the local tolerability via buccal examination after dosing BXCL501 film.
- Describe the PK and exposure of dexmedetomidine as delivered by sublingual BXCL501 dosing.
- Part B: Describe the duration of calming as measured by the 3 supplementary items of the PANSS.

4 STUDY DESIGN

4.1 DURATION OF STUDY

The total duration of the study, excluding Screening, will be approximately seven days (Day 1 through follow-up). The duration of study treatment (BXCL501/placebo) is one day.

4.2 NUMBER OF PARTICIPANTS (STUDY POPULATION)

In Part B a total of 46 subjects will be randomized 1:1 to receive BXCL501 40 µg or matching placebo film (23 subjects on BXCL501 and 23 on placebo).

4.3 DESIGN

Part A of this study is a randomized, double-blind, placebo-controlled, multiple ascending dose study assessing efficacy, PK, safety, and tolerability of BXCL501 dosing in adult (65 years and older) males and females with acute agitation associated with dementia. See the SAP for Part A for more details on Part A study design.

Part B is a parallel group study of 40 µg BXCL501 versus placebo. Forty-six patients in Part B of this study will be randomized in a 1:1 ratio to receive BXCL501 40 µg or matching placebo film. The study will take place at approximately 4 centers in the United States.

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

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

The study will consist of a pre-screening/screening period, treatment period, and a follow-up period.

Patients in Part B of this study will have assessments as outlined in the Schedule of Events (Table 1). The Pre-Screening visit may occur no more than 28 days before first dose of study treatment.

4.3.1 *PRE-SCREENING AND SCREENING PERIOD*

At the Pre-Screening visit, if a subject has orthostatic hypotension (OH) on more than 1 instance in the same day during the 1-week safety observation period, they will be excluded from study participation. Following the 1-week safety observation period, subjects will complete the Screening visit as outlined in the Schedule of Events (Table 1).

4.3.2 *TREATMENT PERIOD*

Upon confirmation of eligibility, Part B subjects will be randomized to receive a single dose of BXCL501 40 µg of or matching placebo film.

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

After pre-dose vitals have been collected, a single dose of BXCL501 or placebo film will be administered sublingually by the patient if able with instructions from an unblinded staff member who will not participate in evaluation of safety or efficacy. The drug film will be retained in the sublingual cavity until dissolved. Participants will also be evaluated for local irritation around the area where the film is placed. Efficacy and safety assessments will be conducted periodically before and after dosing.

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

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on the final study day or upon early termination. For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value

returns to baseline (or within normal limits) or the investigator deems the abnormality to be of no clinical significance. Subjects presenting with a clinically significant urinary tract infection (UTI) as determined by clinical laboratory tests will be excluded from the study.

A nurse will be present prior to dosing and remain present for at least 6 hours after dosing or longer if needed, until any safety concerns, intolerability or adverse events resolve.

The PK plasma samples should be collected per the Schedule of Events (Table 1).

4.3.3 *FOLLOW-UP PERIOD*

The Follow-up Period will encompass the Day 2 Follow-Up and the Day 3 visits as detailed in Table 1.

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

4.4 SCHEDULE OF EVENTS AND ASSESSMENTS

Table 1 presents the schedule of study events and assessments.

Table 1: Schedule of Events

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

Activity	**Pre-Screening[7,8]**	**Screening**	**Pre-Dose[1]**	**Treatment Evaluation Day 1**									**Day 2 Follow-Up (+1 day)**	**Day 3**	**Day 7 (+2 days)**
Time point	**Pre-treatment**	**Pre-treatment**	**-1 hr to time 0**	**5 min**	**10 min**	**15 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**24 hr (-9/+12 hr)**		**End of Study**
Inclusion/Exclusion criteria	X	X	X												
Randomization			X												
CMAI		X	X						X						X
Study drug administration			X												
PAS	X	X	X				X	X	X	X		X	X	X	X
PEC[11]	X		X				X	X	X	X		X	X	X	X
ACES			X					X	X	X		X			
CGI-Severity (agitation)			X						X				X		
CGI-Improvement (change in agitation)							X	X	X	X		X			
C-SSRS	X	X											X		
Buccal (SL) assessment[5]				X	X	X	X		X	X			X		
PK sampling[4]							X	X	X*	X		X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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4.5 TREATMENT

Evaluation of a single dose of BXCL501 40 µg is planned for Part B.

4.6 RANDOMIZATION

Upon confirmation of eligibility, Part B subjects will be randomized to receive a single dose of BXCL501 40 µg of or matching placebo film. Study randomization will be computer generated.

5 OUTCOME VARIABLE DEFINITIONS

5.1 PRE-SCREENING, SCREENING, AND BASELINE CHARACTERISTICS

Pre-Screening: Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight and body mass index (BMI), medical history, prior and concomitant medications, physical examination, resting and orthostatic vital signs, 12-lead electrocardiogram (ECG), clinical laboratory results, urine drug screen, Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR), PAS, PEC, Columbia-Suicide Severity Rating Scale (C-SSRS), and any adverse events will be collected at pre-screening.

Screening: Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight and body mass index (BMI), medical history, prior and concomitant medications, physical examination, resting and orthostatic vital signs, UTI screening, pregnancy test, PAS, C-SSRS, and any adverse events will be collected at screening.

Baseline (Pre-Dose): Inclusion/exclusion criteria, resting and orthostatic vital signs, 12-lead ECG, concomitant medications, CMAI, PAS, PEC, ACES, CGI-S, and adverse events will be collected prior to dose administration.

5.2 EFFICACY ASSESSMENTS

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

5.2.1 *PANSS-EXCITED COMPONENT (PEC)*

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

5.2.2 *PANSS SUPPLEMENTAL ITEMS*

The PANSS Supplementary Items for the Aggression Risk Profile comprises 3 items, each rated on a scale of 1 to 7, with 1 reflecting absence of the emotion/behavior and 7 reflecting extreme emotion/behavior. The specific items

reflect anger, difficulty in delaying gratification, and affective lability. The total score ranges from 3 to 21. This scale is not administered in Part A of the study.

5.2.3 *COHEN MANSFIELD AGITATION INVENTORY (CMAI)*

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

The CMAI Instruction Manual (Cohen-Mansfield, 1989) acknowledges that the CMAI contains a diversified group of behaviors. The authors propose that researchers conduct their own factor analysis because factors depend on the population studied, and researchers need to conceptualize their understanding of these behaviors in order to aggregate the behaviors in a meaningful way. For these reasons, analysis of factors may be conducted, should the data warrant the analysis. The factor analysis would include a determination of the appropriate items to include in each factor, based on the observed data from the study. Factors would most likely include physically aggressive behaviors, physically nonaggressive behaviors, verbally aggressive behaviors, and verbally nonaggressive behaviors.

5.2.4 *AGITATION-CALMNESS EVALUATION SCALE (ACES)*

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

5.2.5 *PITTSBURG AGITATION SCALE (PAS)*

The Pittsburg Agitation Scale (PAS) is an instrument based on direct observations of the patient that is developed to monitor the severity of agitation associated with dementia. There are four Behavior Groups observed (using a 0 to 4-point scale) in the patient, Aberrant Vocalization, Motor Agitation, Aggressiveness, Resisting Care.

5.2.6 *CGI-S AND CGI-I FOR AGITATION*

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

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

Severity of agitation will be assessed based on following scale:

0 = Not assessed

1 = Normal not at all symptomatic

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

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

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

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

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

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

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

The CGI-I scores range from 1 to 7:

0=not assessed (missing),

1=very much improved,

2=much improved,

3=minimally improved,

4=no change,

5=minimally worse,

6=much worse,

7=very much worse

5.3 SAFETY AND TOLERABILITY ASSESSMENTS

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate measured

as pulse, respiratory rate, and temperature), ECG, and physical examination findings.

5.3.1 *ADVERSE EVENTS*

An adverse event (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.

New conditions detected or diagnosed after study intervention administration meet the definition of an AE even though they may have been present before the start of the study.

Adverse events with an onset following exposure to study treatment (during the BXCL501 treatment phase) or AEs already present that worsen in intensity or frequency following exposure to study treatment are considered treatment emergent adverse events (TEAEs).

5.3.2 *COLUMBIA SUICIDE SEVERITY RATING SCALE*

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

5.3.3 *LABORATORY SAFETY ASSESSMENTS*

Samples for the following laboratory tests will be collected at the timepoints specified in the Schedule of Events (Table 1).

Hematology:	Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serum chemistry:	Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose, albumin, and total protein
Urinalysis:	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test:	Conducted by local labs

Urine Drug Screen:	Cocaine, amphetamine, phencyclidine, benzodiazepines, marijuana. (Note: Marijuana positive is allowed provided subject is not moderately to severely dependent, benzodiazepine positive are allowed if prescribed)

5.3.4 *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 timepoints specified in the schedule of events. Measurements should be made at least 1 minute apart using the same arm at each visit.

At indicated timepoints orthostatic measurement of systolic, diastolic blood pressure and heart rate will be measured after the subject has been standing for a total of 5 minutes. Temperature and respiratory rate will be recorded when standing 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

5.3.5 *ELECTROCARDIOGRAM*

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

5.3.6 *PHYSICAL EXAMINATION*

A standard physical examination will be performed at Pre-Screening, Screening and 24 hours post dose. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at Screening and weight will be measured again at the Day 2 follow-up visit.

5.3.7 *BUCCAL ASSESSMENTS*

Buccal (SL) exam for local irritation and time to disappearance of the film will be performed by unblinded staff at 5, 10, 15, 30 min, 2 hr, 4 hr and 24 hr post first dose.

5.4 CLINICAL DIAGNOSIS AND DESCRIPTION OF DEMENTIA

The subtype of dementia will be determined and recorded based upon clinical neurologic and psychiatric evaluation to include review of all available medical information, medical records, documentation of prior evaluations, family/caretaker interviews, records, laboratory, genetics or other biomarkers, and results of neuroimaging (if available).

The following scales will characterize subject's dementia (*DSM-5* Major Neurocognitive disorder) in terms of cognitive and functional impairment. Both assessments will occur at the Pre-Screening and Day 2/Follow-Up visits.

5.4.1 *MMSE*

The Folstein Mini-Mental State Examination (MMSE) is an exam that tests an elderly person's cognitive ability. Domains measured by the MMSE include orientation to time and place, registration, attention and calculation, recall, naming, repetition, comprehension, reading, writing, and drawing. Total points on this test is 30. Any score of 24 or more (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.

5.4.2 *CDR*

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

CDR-0 = normal

CDR-0.5 = very mild dementia

CDR-1 = mild

CDR-2 = moderate

CDR-3 = severe

5.5 PHARMACOKINETICS

For each subject, up to 6 blood samples (24 mL of blood) will be collected during the study for PK analysis. Blood samples (4 ml) will be collected at 0.5, 1, 2, 4, 8, and 24 hours post-dose per Table 1 Schedule of Events. A sample may not be collected if the physician in charge of the patient indicates in the source

documents that the patient is in a mental state that is not conducive to PK sample collection and record the PEC score at the time of proposed sample collection.

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

For Part B subjects, an additional sample will be collected if possible, between 10 and 12 hours per the Schedule of Events.

5.6 CONCOMITANT MEDICATIONS

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

6 STUDY ENDPOINTS

6.1 PRIMARY ENDPOINTS

6.1.1 *PRIMARY EFFICACY ENDPOINT*

- Change in PEC total score from baseline

6.1.2 *PRIMARY EFFICACY TIMEPOINT*

- 2 hours post-dose

6.1.3 *PRIMARY SAFETY AND TOLERABILITY ENDPOINTS*

- Comparison of cardiovascular parameters (BP, HR, pulse oximetry, ECG) between BXCL501 40 µg and placebo

6.2 SECONDARY ENDPOINTS

6.2.1 *SECONDARY EFFICACY ENDPOINTS*

- Change in PEC total score from baseline at 30 min, 1 hr, 4 hr, and 8 hr post-dose, and at Day 2, Day 3, and Day 7
- Percentages of subjects at each dose who achieve a 40% reduction from baseline in PEC total score at 2 hr post-dose (“Responders”)
- Change in PAS total score from baseline at 30 min, 1 hr, 2 hr, 4 hr, and 8 hr post-dose, and at Day 2, Day 3, and Day 7
- Change in ACES score from baseline at 1 hr, 2 hr, 4 hr, and 8 hr post-dose
- Change in CGI-S agitation score from baseline at 2 hr post-dose and at Day 2
- CGI-I agitation score at 30 min, 1 hr, 2 hr 4 hr, and 8 hr post-dose
- Change in CMAI total score from baseline at 2 hr post-dose and Day 7

6.2.2 *SECONDARY SAFETY AND TOLERABILITY ENDPOINTS*

- Time taken for medication to dissolve (1-30 sec, 31-59 sec, 1-2 min, 3+ min) – only assessed at 30 minutes
- Negative reaction to the sublingual film in the examiner's opinion (Yes/No) – assessed at 30 min, 2 hr, 4 hr, and 24 hr post-dose
- Part B: Duration of calming, as measured by the PANSS supplementary items. All timepoints will be included, with the 2 hour timepoint of primary interest.

6.2.3 *SECONDARY PHARMACOKINETIC ENDPOINTS*

PK analyses will be specified in a separate document.

6.3 EXPLORATORY ENDPOINTS

- CCI [redacted]

7 STATISTICAL ANALYSES

Statistical analyses will be performed using SAS® software version 9.4.

7.1 STATISTICAL METHODOLOGY

7.1.1 *SAMPLE SIZE DETERMINATION*

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7.1.2 *POPULATIONS FOR STATISTICAL ANALYSIS*

The following are analysis populations for the study:

- Safety Population: All subjects who receive study drug, according to the treatment received. The Safety Populations from both Parts A and B will be combined. Select tables may be generated for the Part B Safety Population only.
- Intent to treat (ITT) Population: All Part B subjects in the Safety Population, analyzed as randomized.
- Per Protocol (PP) Population: All subjects in the Part B ITT Population with no major protocol deviations likely to impact inference. PP analyses may not be conducted if there are not sufficient protocol deviations deemed to impact analysis. If subjects receive treatment other than to which they were randomized, they will be included in a PP analysis as treated (barring

protocol deviations sufficient to exclude them for other reasons). The PP population will be finalized prior to breaking the blind for Part B.

7.1.3 *STATISTICAL ANALYSES – GENERAL CONSIDERATIONS*

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). The same number of decimal places as in the raw data will be presented when reporting minimum and maximum. One more decimal place than in the raw data will be presented when reporting mean and standard deviation.

For categorical variables, frequencies and percentages will be presented by treatment.

Baseline is defined as the last non-missing observation prior to initiation of study medication.

All statistical testing will be based on a two-sided significance level of 0.05 unless otherwise stated.

Listings for Appendix 16.2 in the CSR will include all the subject data points being collected or derived for analyses. Data listings will be provided for all subjects up to the point of withdrawal.

7.1.4 *PROCEDURES FOR HANDLING MISSING DATA*

No imputation will be performed for missing data unless stated otherwise. For longitudinal analyses of continuous data, the Mixed Model Repeated Measures is considered valid under a Missing at Random (MAR) missingness mechanism. Furthermore, no missing data is anticipated for the primary endpoint (PEC) at the primary timepoint of 2 hours.

7.1.5 *INTERIM ANALYSES*

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

7.2 SCREENING AND BASELINE CHARACTERISTICS

Summary tables will be constructed by treatment for the Safety Population for Parts A and B combined for the following Pre-Screening, Screening or Pre-Dose data: demographic characteristics of age, sex, race, ethnicity, weight, height and body mass index (BMI), medical history, prior medications, laboratory examinations, vital signs, and ECG.

Listings will be provided for eligibility criteria violations, demographics, and medical history.

7.3 SUBJECT DISPOSITION

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population

by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment. Subject-level listings will be provided.

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR.

7.4 STUDY TREATMENT ADMINISTRATION

Study drug administration data will be listed by subject.

7.5 EFFICACY ANALYSES

The efficacy analyses described in this section compare the 40 µg BXCL501 group to the placebo group. Nominal significance levels will be reported with no adjustment for secondary endpoints. However, PEC total scores at earlier timepoints will be tested hierarchically to determine earliest onset of action, conditional upon the significance of differences between 40 µg and placebo at 2 hours.

The intent to treat population will be considered primary. Observations recorded after use of rescue medication will be censored (considered missing).

7.5.1 *PRIMARY EFFICACY ANALYSIS*

The primary efficacy endpoint is change from baseline in PEC total score. The primary efficacy timepoint will be at 2 hrs. post-dose.
A mixed model for repeated measures (MMRM) will be used to assess treatment group differences for change from baseline. Change from baseline scores will include all available timepoints in a single model; the 2 hr timepoint is considered primary, and all other timepoints are considered secondary. Fixed effects will include treatment group, analysis visit, treatment-by-visit interaction, and a baseline-by-visit interaction. Visit will be fit as a repeated effect in the model using the repeated statement in SAS. The baseline score will be included as a continuous covariate. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a Toeplitz structure will be used.

Least squares (LS) means will be presented for treatment at each timepoint in summary tables. Pair-wise comparisons of differences in LS means, two-sided 95% confidence intervals (CIs) on differences, and p-values will be provided for treatment versus placebo for each visit. Line graphs will be provided reflecting LSM changes from baseline over time.

Individual patient scores for the PEC for all timepoints will be provided in a listing.

7.5.2 *SECONDARY EFFICACY ANALYSES*

Changes from baseline for PAS, ACES, CGI-S agitation score, and CMAI total score for all available timepoints will be analyzed using MMRM, using the specifications described above. CGI-I agitation score will be compared between treatment and placebo groups using MMRM, however as there is no baseline measurement, it will not be included in the model. Listings will be provided for individual patient scores. Line graphs will be provided reflecting changes from baseline over time in PAS score.

Responder (ie, percentage change from baseline in the PEC score at 2 hours >40%) comparisons will be made via Fisher's Exact test. Nominal p-values and the treatment difference and associated two-sided 95% confidence interval will be based on the Wald method with continuity correction and reported for BXCL501 versus placebo. A bar chart will be provided reflecting percentages of responders at each timepoint for the BXCL501 group and placebo.

For the CGI-S and CGI-I, scores of 0 (not assessed) will be set to missing prior to analysis.

7.5.3 *EXPLORATORY EFFICACY ANALYSES*

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7.6 SAFETY ANALYSES

Safety analyses will be based on the Safety Population for Parts A and B combined. Safety and tolerability will be assessed by clinical review of all safety parameters including AEs, laboratory values and vital signs. The safety analyses will include all results collected from randomization through the end of the study.

7.6.1 *PRIMARY SAFETY ANALYSES*

Comparison of cardiovascular parameters (BP, HR) between BXCL501 40 µg and placebo.

7.6.2 *SECONDARY SAFETY ANALYSES*

A frequency summary will be presented for time taken for medication to dissolve at 30 minutes (1-30 seconds, 31-59 seconds, 1-2 minutes, 3+ minutes) and for negative reaction to sublingual film (Yes/No) assessed at 30 min, 2 hr, 4 hr, and 24 hr post-dose. These parameters will be presented for each treatment group at

each timepoint. Listings will include subject-level findings as well as all physical findings noted during buccal examinations.

7.6.3 *ADVERSE EVENTS*

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 23.1) coding system and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized by severity as well as relationship to Study Medication. For summaries by relationship, relationship will be categorized as related (unlikely, possibly, probably, and definitely related) or not related.

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to Study Medication when summarized by relationship. If a patient reports multiple preferred terms for a system organ class, the patient will be counted only once for that system organ class.

Proportions for adverse events that are gender-specific (e.g., dysmenorrhea) will be based on the number of patients from that gender.

The number and percentage of patients who experience TEAEs will be summarized by treatment group for the following:

- By system organ class and preferred term
- By severity, system organ class, and preferred term
- By relationship to Study Medication (related, not related), system organ class, and preferred term
- Serious adverse events by system organ class and preferred term
- Serious adverse events by relationship to Study Medication, system organ class, and preferred term
- Adverse events resulting in discontinuation of Study Medication by system organ class and preferred term

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

7.6.4 *COLUMBIA SUICIDE SEVERITY RATING SCALE*

The C-SSRS data will be summarized descriptively. Individual patient data will be provided in a listing. Only the following specific suicidal ideation and behavior category questions with any "Yes" responses will be summarized in a frequency distribution table at each post-randomization visit:

- Any Suicidal Ideation Category:
    - Wish to be Dead
    - Non-Specific Active Suicidal Thoughts
    - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
    - Active Suicidal Ideation with Specific Plan and Intent
- Any Suicidal Behavior Category:
    - Completed Suicide
    - Non-Fatal Suicide Attempt
    - Interrupted Attempt
    - Aborted Attempt
    - Preparatory Acts or Behavior
    - Any Suicidal Ideation or Behavior Category

7.6.5 *CLINICAL LABORATORY EVALUATIONS*

Each laboratory value and change from baseline (when appropriate) will be summarized for hematology, blood chemistry and urinalysis for each treatment and all available timepoints. Individual patient listings will be provided.

7.6.6 *PULSE OXIMETRY*

A listing of findings from pulse oximetry will be provided by subject.

7.6.7 *PHYSICAL EXAMINATION*

A listing of abnormal physical examination findings will be provided by subject. Pregnancy, alcohol screening, and drug testing results will be provided by patient.

7.6.8 *CLINICAL DIAGNOSIS AND DESCRIPTION OF DEMENTIA*

MMSE and CDR scores will be listed by patient.

7.6.9 *VITAL SIGNS*

Resting, standing, and postural change (where available) vital signs will be summarized at each timepoint for each treatment group, using descriptive statistics. For any vital signs measured in triplicate, only the 2nd measurement will be included in the descriptive statistics. Change from baseline in vital signs values will also be summarized, as well as abnormal categorical postural changes in blood pressure (systolic blood pressure postural decrease > 20 mmHg or diastolic blood pressure postural decrease > 10 mmHg). Individual patient listings will be provided.

Postural change in vital signs (commonly referred to as “orthostatic”) is defined as the change from the resting to standing positions.

Baseline will be defined as the last vital sign value obtained before the first dose of Study Medication on Day 1.

7.6.10 *12-LEAD ELECTROCARDIOGRAM*

The change from baseline in ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

In addition, the number of subjects meeting the following criteria will be presented for each treatment at each time point:

ECG Mean Heart Rate (beats/min):

- Decrease in HR from baseline >25% to a HR <50 bpm
- Increase in HR from baseline >25% to a HR >100 bpm

PR Interval, Aggregate (msec):

- Increase in PR from baseline >25% to a PR >200 msec

QRS Duration, Aggregate (msec):

- Increase in QRS from baseline >25% to a QRS >120 msec

QTcF Interval, Aggregate (msec):

- QTcF <=450 msec
- QTcF >450 to <=480 msec
- QTcF >480 to <=500 msec
- QTcF >450 msec
- QTcF >480 msec
- QTcF >500 msec
- ΔQTcF <=30 msec
- ΔQTcF >30 to <=60 msec
- ΔQTcF >60 msec

In addition, shift tables comparing QTcF interval categories from baseline to each post-baseline time point will be provided by treatment group for the following:

- <=450 msec
- >450 msec to <=480 msec
- >480 msec to <=500 msec
- >500 msec

For the above tables, a category for baseline missing will be included, as needed.

7.6.11 *CONCOMITANT MEDICATIONS*

Concomitant medications will be summarized (n and %) by ATC class and preferred term (coded by WHO Drug coding dictionary September 2020) for each treatment group. Concomitant medications for individual patients will be provided in a listing.

7.6.12 *RESCUE MEDICATIONS*

Subjects needing rescue medications will be summarized (n and %) by time interval (eg, 0 to <2 hours) to first use of rescue medication for each treatment group. Rescue medications for individual patients will be provided in a listing.

7.6.13 *STUDY MEDICATION COMPLIANCE*

Study Medication compliance will be measured by the number of days of Study Medication administered and the percentage of scheduled doses that were taken. Descriptive statistics will be used to summarize dosing compliance within each treatment group, as well as provided in a listing per patient.

7.7 PHARMACOKINETIC and PHARMACODYNAMIC ANALYSIS

PK analyses will be specified in a separate document. Data from subjects who participated in the study will be included in the pharmacokinetic analysis. Subjects with missing sample concentrations will be included in the pharmacokinetic analyses provided their pharmacokinetic parameters can be adequately characterized based upon the remaining data.

Deviation from procedures described in this protocol that impact the quality of data required to meet the objectives of the study will be documented and may result in exclusion of pharmacokinetic data from the analyses for a subject. This includes any deviations or events that would invalidate the evaluation of the pharmacokinetics. Examples of deviations and events which could result in exclusion of pharmacokinetic data from the analyses include emesis, immediately after dosing (within a predetermined time, to be specified in the SAP for PK and PK/PD analyses), sample processing or assay errors that lead to inaccurate bioanalytical results. Other deviations or events, which do not disqualify data from analyses, may require minor adjustments to calculations. If

these occur, data analyses will be adjusted and documented accordingly such that conclusions are not biased. An example of such an event includes, but is not limited to, minor deviations between the actual and scheduled time of sample collection.

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

Other PK analyses may be performed as appropriate.

Pharmacodynamic data, including changes in blood pressure & heart rate, and changes in measures of agitation, from baseline may be evaluated as a function of time and as a function of measured or estimated plasma concentrations. Details will be described in the SAP for PK and PK/PD analyses.

8 REFERENCES

Cohen-Mansfield J, Marx MS, & Rosenthal AS. (1989). A description of agitation in a nursing home. *Journal of Gerontology: Medical Sciences*, 44(3), M77-M84.

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

9 TABLES, LISTINGS AND FIGURES

A separate document containing the list of tables, listings, and figures (TFLs) to be included in the post-text Appendix 14 of the CSR will be provided. TFLs may be modified with Sponsor's approval and as deemed necessary without update to the SAP.