STATISTICAL ANALYSIS PLAN

PROTOCOL: BXCL501-201

A Phase 1b/2 Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Study of BXCL501 to Treat Symptoms of Acute Opioid Withdrawal in Patients with Opioid Use Disorder Who are Physically Dependent on Opioids

SPONSOR: BioXcel Therapeutics, Inc.
555 Long Wharf Drive
12th Floor
New Haven, CT 06511

PRODUCT: BXCL501

AUTHORS: [redacted]
Cognitive Research Corporation
200 Central Ave. Suite 1230
Saint Petersburg, Florida 33701

[redacted]
Cognitive Research Corporation
200 Central Ave. Suite 1230
Saint Petersburg, Florida 33701

DATE: 02 December 2020

STATUS: Final Version 2.0

Statistical Analysis Plan
Protocol: BXCL501-201
Final Version: 2.0 Date: 2 December 2020

CRC REPRESENTATIVE

DOCUMENT REVIEWED AND APPROVED BY:

[redacted]

STATISTICAL CRO REPRESENTATIVE

DOCUMENT REVIEWED AND APPROVED BY:

[redacted]

SPONSOR COMPANY REPRESENTATIVE

DOCUMENT REVIEWED AND APPROVED BY:

[redacted]

TABLE OF CONTENTS

AMENDMENT HISTORY

Amendment #1: Summary of Changes

The following lists changes to the SAP from the previous version (BXCL501-201 SAP Final v1.0_10Jun2020)

Section	Change
General	Change “patients” to “participants”
General	Renumber Tables, Listings, and Figures; add tables for morphine stabilization phase
General	Add language allowing for additional cohorts to be added to study
Title	Change study phase in title to 1b/2, to reflect protocol Administrative Letter 03 (10Jun2020)
2 (Introduction)	Add Administrative Letter 03
3.2 (Secondary Objectives)	Specify unit for time to dropout after opioid discontinuation (hours)
Table 1 and 5.3.5 (Electrocardiogram)	Modified time points for ECG assessments, based on Administrative Letter 03
5.2.1 (Short Opiate Withdrawal Scale of Gossop)	Add language specifying how total score is calculated
5.3.1 (Adverse Events)	Add definition of treatment-emergent adverse events
5.5 (Concomitant Medications)	Add definition of con meds
6.2 (Secondary Efficacy Endpoints)	Remove change from baseline for ACES endpoint
6.3 (Exploratory Efficacy Endpoints)	Move bullet describing analyses for morphine maintenance phase (Days 1-5) to separate section
7.5 (Efficacy Analyses)	Remove language regarding censoring observations after rescue medication
7.5.1 (Primary Efficacy Endpoint)	Clarify language, add Screening as a covariate in mixed model, remove treatment as a main effect from model, remove baseline*visit interaction from model
7.5.2 (Secondary Efficacy Endpoints)	Clarify language; modify analyses for ACES to eliminate baseline; change Cox regression to log rank; change logistic regression to Fisher’s Exact test
7.5.4 (Additional Analyses)	Add analyses for data from the morphine stabilization phase
7.6 (Safety Analyses)	Clarify/simplify language (not substantive)
7.6.1 (Adverse Events)	Remove language re: gender-specific denominators

Section	Change
7.6.7 (12-Lead Electrocardiogram)	Replace frequency distribution with shift tables; modify QTcF intervals of interest
7.6.8 (Concomitant Medications)	Add indication of rescue medications in summary table
7.6.9 (Study Medication Compliance)	Change heading and text to reflect study medication exposure instead of compliance
7.6.11 (Comparison of Cardiovascular AEs)	Removed entire section; routine significance testing on AEs of special interest will not be conducted due to concerns with alpha level inflation

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACES	Agitation-Calmness Evaluation Scale
AE	Adverse event
BAL	Breath alcohol level
BID	Twice a day
BMI	Body mass index
BP	Blood pressure
COWS	Clinical Opiate Withdrawal Scale
CRO	Contract research organization
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HR	Heart rate
hr	Hour
FAS	Intent to treat
kg	Kilogram
µg/µcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minutes
MINI	Mini-International Neuropsychiatric Interview
mL	Milliliter
mm	Millimeters
mmHg	Millimeters of mercury
MMRM	Mixed model repeated measures
OUD	Opioid use disorder
PI	Principal investigator
PK	Pharmacokinetic
PP	Per protocol

Abbreviation	Definition
QID	Four times a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SL	Sublingual
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
SP	Safety population
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, figures, and listings
TLFB	Timeline Followback
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled “A Phase 1b/2 Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Study of BXCL501 to Treat Symptoms of Acute Opioid Withdrawal in Patients with Opioid Use Disorder Who are Physically Dependent on Opioids” (V2 08 May 2020; Administrative Letter 01, 27May2020; Administrative Letter 02, 29May2020; Administrative Letter 03, 10June2020). All planned pharmacokinetic (PK) analyses will be described in a separate PK 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 establish the safety and tolerability of ascending doses of BXCL501 relative to placebo in subjects with opioid use disorder who are physically dependent on opioids and maintained on oral morphine.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this trial are to establish the efficacy of BXCL501 relative to placebo in improving the following:

- Opioid withdrawal symptoms:
  - Short Opiate Withdrawal Scale of Gossop (SOWS-GOSSOP) and
  - Clinical Opiate Withdrawal Scale (COWS)
- Time to dropout after opioid discontinuation (in days)
- Percentage of subjects dropping out after opioid discontinuation
- Assessment of safety reflected by scores on the Agitation and Calmness Evaluation Scale (ACES) assessment

3.3 EXPLORATORY OBJECTIVE

[redacted].

4 STUDY DESIGN

4.1 DURATION OF STUDY

The total duration of the study, excluding the 30-day Screening, will be approximately 21 days (Day 1 through follow-up). Days 1-5 will comprise the stabilization phase, during which all study participants will be administered morphine. On Day 6, participants will be randomized to either BXCL501 or

placebo. Days 7-12 will represent the treatment phase (BXCL501/placebo). Days 13-14 will be the post-treatment or early termination phase. The follow-up period will occur on Day 21.

4.2 NUMBER OF PARTICIPANTS (STUDY POPULATION)

A total of 5 cohorts will be tested. Each cohort will include 25 subjects, randomized 4:1 to BXCL501 or placebo (20 BXCL501 and 5 placebo), for a total of 125 subjects (100 BXCL501 and 25 placebo). Additional cohorts may be added. The study will be conducted at up to 4 sites.

4.3 DESIGN

This is an inpatient Phase 1b/2 randomized, double-blind, placebo-controlled, ascending dose study of BXCL501 to treat symptoms of acute opioid withdrawal in subjects with opioid use disorder who are physically dependent on opioids. The study will assess the safety, pharmacokinetics, and early signs of efficacy of escalating doses of BXCL501 versus placebo following discontinuation of morphine maintenance in adults (≥18 to <65 years of age).

After a 30-day screening period, eligible male and female adult subjects with OUD who are physically dependent on opioids will be admitted to an inpatient unit. The morphine maintenance phase will begin on Study Day 1 and continue until the end of Study Day 5. Total of 5 cohorts (total N=125) will be tested. In each cohort, approximately 25 subjects will receive oral morphine. The total dose of morphine during the first two days of stabilization (Study Days 1-2) can vary at the discretion of the investigator, between 120 mg and 150 mg per day depending on participants abuse history and need for higher dose to stabilize withdrawal symptoms. During the next three days (Study Days 3-5), all subjects will receive a standard dose of morphine (30 mg QID) totaling 120 mg in a day. In addition, these subjects will receive placebo films approximately 12 hours apart during the opioid maintenance phase (ie, Days 1-5) to simulate and thus blind treatment with BXCL501 during Days 6-12. Abrupt discontinuation of active morphine will begin on Day 6.

On Study Day 6, subjects will be randomized to receive either placebo or BXCL501 administered approximately 12 hours apart at approximately 8am and 8pm. Placebo or BXCL501 will be administered on Days 6-12. The AM dose will be administered at the same time each day (±30 minutes) and the second dose will be administered 12 hours later with a ± 30-minute window. Study participants can only be given the second dose if they are hemodynamically stable, not hypotensive (must be greater than 110/70 diastolic/systolic) and not bradycardic (must be greater than 55 bpm). Participants also cannot be given the second dose of BXCL501 if they are orthostatic (a drop of 20 points in either SBP or 10 points in DBP) or if they are experiencing an AE that when assessed by the PI precludes redosing. If a subject experiences SBP <90 mmHg; or DBP <60 mmHg; or HR <50 bpm, immediately prior to the next dose, the study team will hold administration of the study medication for that participant until resolution of

these BP and HR parameters. The administration hold will not exceed 2 hours. A total of 5 cohorts will be tested (n=25 per cohort), with the option to add additional cohorts. Within each cohort, 20 subjects will receive active BXCL501 and 5 subjects will receive placebo. The following doses will be administered: 30 µg (Cohort 1), 60 µg (Cohort 2), 90 µg (Cohort 3), 120 µg (Cohort 4), and 180 µg (Cohort 5). Safety and tolerability will be monitored continuously and summarized upon completion of each cohort by medical safety review. Studies of opioid withdrawal with placebo arms are likely to have high dropout rates, thus, the dropouts prior to Day 6 may be replaced to ensure enough sample size entering the treatment phase. The study is intended to be flexible and adaptable and as such, the dosing frequency, the doses and the number of cohorts of BXCL501 may be changed as a result of review of safety, tolerability and efficacy data.

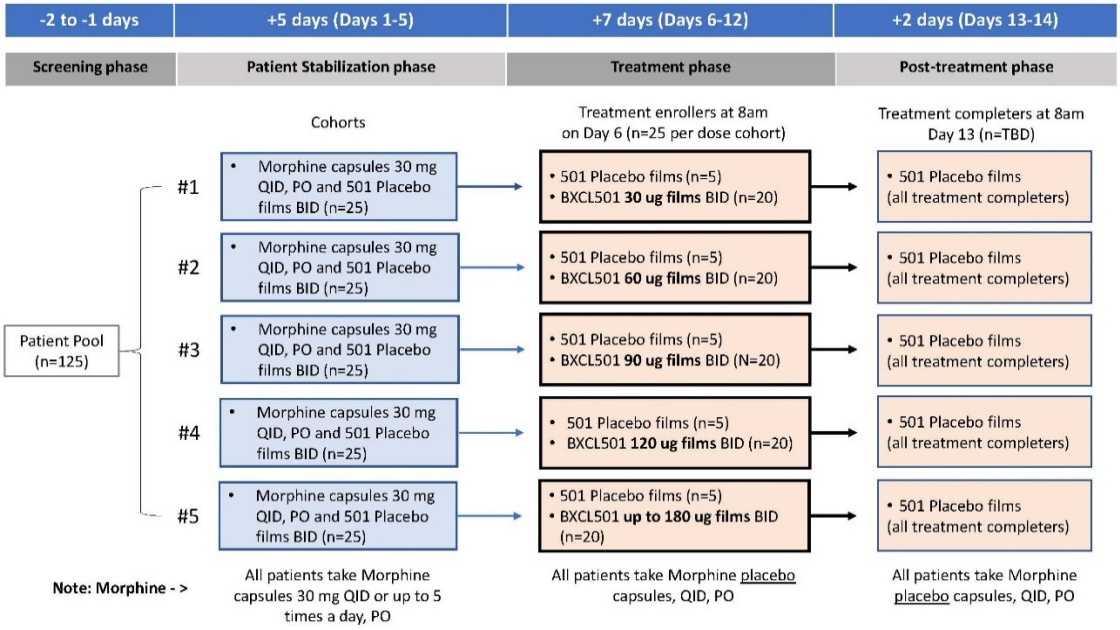
Opioid withdrawal symptoms (SOWS-Gossop and COWS) will be measured throughout the inpatient period at pre-dose, 2 hours post-dose, pre-2nd dose and 2 hours post-second dose. Additional/SOWS-Gossop/COWS may be administered at investigator discretion. Transition to treatment for opioid use disorder will be offered prior to participantss leaving the unit.

Safety and tolerability assessments will be continued until the morning of Day 14 (day of discharge).

Overall agitation and sedation will be evaluated with the Agitation-Calmness Evaluation Scale, 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.

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

4.4 STUDY SCHEMA



BID = twice a day; PO = oral/by mouth; QID = four times a day

4.5 SCHEDULE OF EVENTS AND ASSESSMENTS

Table 1 presents the schedule of study events and assessments.

Table 1: Schedule of Events

		Inpatient Admission (14 days)				
			Detoxification			
	Screening[1]	Morphine maintenance	Randomization & first day of treatment	Treatment Phase	Post Treatment phase or ET	One-week Follow-up
Day	-2 to -1	Days 1 - 5	Day 6	Days 7 - 12	Days 13-14	Day 21 (± 3 days)
Naloxone Administration[2]		X				
Informed Consent	X					
Inclusion/Exclusion Criteria[3]	X		X			
Mini International Neuropsychiatric Inventory (MINI)	X					
Columbia Suicide Severity Rating Scale (C-SSRS)	X					
Randomization (Day 6)			X			
Demographics	X					
Medical and Psychiatric History	X					
Concomitant Medications	X	X	X	X	X	X
Physical Exam[4]	X	X		X	X	
12-Lead ECG[5]	X	X	X	X	X	
Safety labs	X		X			X
Vital Signs Measurements[6]	X	X	X	X	X	X
Buccal SL assessment[7]		X	X	X	X	
Rapid Urine Pregnancy Testing[8]	X	X	X			
AE Monitoring	X	X	X	X	X	X
Urine Toxicology/BAL[9]	X	X	X	X		X
Timeline Followback	X					X
Pharmacokinetics[10]			X	X[11]		
SOWS & COWS[12]	X	X	X	X	X	
Administration of Morphine		X				
Administration of BXCL501 or Placebo[13]			X	X		
Administration of Morphine Placebo[14]			X	X	X	
Administration of BXCL501 Placebo and Morphine Placebo					X	

Agitation and Calmness Evaluation Scale (ACES)[15]		X	X	X		

Notes to the Schedule of Events:

4.6 TREATMENT

Following the morphine stabilization phase, the following doses of BXCL501 will be administered to subjects randomized to active treatment: 30 µg (Cohort 1), 60 µg (Cohort 2), 90 µg (Cohort 3), 120 µg (Cohort 4), and 180 µg (Cohort 5), with the option to add additional cohorts.

On Study Day 6, subjects will be randomized to receive either placebo or BXCL501 administered approximately 12 hours apart at approximately 8am and 8pm. Placebo or BXCL501 will be administered on Days 6-12. The AM dose will be administered at the same time each day (±30 minutes) and the second dose will be administered 12 hours later with a ± 30 minute window. Study participants can only be given the second dose if they are hemodynamically stable, not hypotensive (must be greater than 110/70 diastolic/systolic) and not bradycardic (must be greater than 55 bpm). Study participants also cannot be given the second dose of BXCL501 if they are orthostatic (a drop of 20 points in either SBP or 10 points in DBP) or if they are experiencing an AE that when assessed by the PI precludes redosing. If a subject experiences SBP <90 mmHg; or DBP <60 mmHg; or HR <50 bpm, immediately prior to the next dose, the study team will hold administration of the study medication for that participant until resolution of these BP and HR parameters. The administration hold will not exceed 2 hours.

The study is intended to be flexible and adaptable and as such, the dosing frequency, the doses and the number of cohorts of BXCL501 may be changed as a result of review of safety, tolerability and efficacy data.

4.7 RANDOMIZATION

Upon confirmation of eligibility, subjects will be randomized to BXCL501 or placebo film. In each of the 5 dose cohorts, 25 participants (20 drug-treated, 5 placebo) will be randomized 4:1 BXCL501 film: Placebo. Study randomization will be computer generated.

5 OUTCOME VARIABLE DEFINITIONS

5.1 SCREENING, STABILIZATION, AND BASELINE CHARACTERISTICS

Screening: Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight and body mass index (BMI), medical and psychiatric histories, prior and concomitant medications, physical examination, resting and orthostatic vital signs, 12-lead ECG, pregnancy test, blood and urine sample collection for clinical laboratory tests, Timeline Followback (TLFB), COWS, SOWS, MINI, C-SSRS, and any adverse events will be collected at Screening.

Stabilization: The SOWS, COWS, naloxone challenge (if COWS <6), pregnancy test, resting and orthostatic vital signs, urine samples for laboratory tests, physical examination, 12-lead ECG, concomitant medications, ACES, buccal

assessment for local irritation, and any adverse events will be collected at Day 1. The SOWS, COWS, ACES, resting and orthostatic vital signs, urine toxicology, 12-lead ECG, concomitant medications, and adverse events will be collected on each of Days 2-5.

Baseline (Pre-Dose): Inclusion/exclusion criteria, SOWS, COWS, ACES, resting and orthostatic vital signs, 12-lead ECG, concomitant medications, pregnancy test, blood and urine samples for laboratory tests, urine toxicology, plasma samples for PK analysis, buccal assessment for local irritation, 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 *SHORT OPIATE WITHDRAWAL SCALE OF GOSSOP (ALSO - GOSSOP)*

The SOWS-Gossop is a 10-item patient reported measure designed to measure the symptoms of withdrawal in subjects who are dependent on opioids (Gossop, 1990). Each of the 10 items represents a symptom: “Feeling Sick,” “Stomach Cramps,” “Muscle Spasms/Twitching,” “Feeling of Coldness,” “Heart Pounding,” “Muscular Tension,” “Aches and Pains,” “Yawning,” “Runny Eyes,” and “Insomnia/Problems Sleeping.” Subjects evaluate the severity of each symptom over the last 24 hours by selecting either as “None,” “Mild,” “Moderate,” or “Severe.”

The SOWS-Gossop total score ranges from 0 to 30, with higher scores indicating greater severity of withdrawal symptoms. Total score is the sum of the individual item scores. “Peak” scores refer to the higher of the two planned post-dose scores within each study day (2 hr post-first dose, 2 hr post-second dose). Average scores refer to the average of the two planned post-dose scores within each study day.

SOWS-Gossop is also referred to as SOWS in this document.

5.2.2 *CLINICAL OPIATE WITHDRAWAL SCALE*

The COWS is an 11-item questionnaire designed to measure a patient’s level of opiate withdrawal (Wesson and Ling, 2003). Symptoms evaluated include resting pulse rate, sweating, restlessness, pupil size, bone or joint aches, runny nose or tearing, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh. COWS total scores range from 0 to 48; scores 5 to 12 are mild, 13 to 24 are moderate, 25 to 36 are moderately severe, and over 36 are severe withdrawal.

"Peak" scores refer to the higher of the two planned post-dose scores within each study day (2 hr post-first dose, 2 hr post-second dose). Average scores refer to the average of the two planned post-dose scores within each study day.

5.2.3 *AGITATION AND CALMNESS EVALUATION SCALE*

Overall agitation and sedation will be evaluated with the Agitation-Calmness Evaluation Scale, (a single item scale) 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.

Administration of the ACES will occur at approximately two hours after BXCL501 or placebo dosing (approximately 10am and 10pm).

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.

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 Screening.

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 for females of childbearing potential only
Urine Drug Screen:	Opioids, methadone, fentanyl, buprenorphine, cocaine, amphetamine, phencyclidine, and ketamine, benzodiazepines, marijuana.
Breath alcohol level	Conducted at Screening, on Study Day 1, and at the follow-up visit.

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 sitting or supine position for at least 5 minutes at the time points specified in the Schedule of Visits and Assessments. Measurements should be made at least 1 minute apart using the same arm at each visit.

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

If the first measurement of vital signs (SBP, DBP and pulse) shows the following, vital signs will be measured again in triplicate (same arm, separated by at least 1 minute) for SBP <110 mmHg, DBP <70 mmHg, and pulse <55 bpm.

5.3.5 *ELECTROCARDIOGRAM*

A 12-lead ECG with rhythm strip will be performed at Screening, pre-morning dose of BXCL501-placebo on Days 1- 5, pre-morning dose on Days 6, 8, 10, and pre-morning dose of BXCL501-placebo on Days 13-14/discharge.

5.3.6 *PHYSICAL EXAMINATION*

A standard physical examination will be performed at Screening, on Study Day 1, and at discharge from the inpatient facility. 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 on the day of discharge.

5.3.7 *TIMELINE FOLLOWBACK*

The Timeline Followback is a method that can be used as a clinical and research tool to obtain a variety of quantitative estimates of marijuana, cigarette, and other drug use. The questionnaire will be used in this study (Sobell, 1996). The TLFB will be administered by an interviewer, self-administered, or administered by computer. It involves asking subjects to retrospectively estimate their drug, marijuana or cigarette use 7 days to 2 years prior to the interview date.

5.3.8 *BUCCAL ASSESSMENTS*

A buccal exam will be conducted at 30 min post- first dose for signs of local irritation on Days 1, 6, and 12, and prior to discharge on Day 14. An additional buccal exam may be done at investigator's discretion or in case of a relevant adverse event.

5.4 PHARMACOKINETICS

Blood samples (4 ml) will be collected at 0, 2, 6, and 12 hours after the first dose of BXCL501 on Study Days 6 and 12. The 12 hr sample will be taken just before the administration of the next dose of BXCL501 or placebo.

5.5 CONCOMITANT MEDICATIONS

Concomitant medications are any medications received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date. Concomitant medications will be reviewed and documented each day during the study.

6 STUDY ENDPOINTS

All efficacy endpoints will be compared between the BXCL501 treatment groups and placebo.

6.1 PRIMARY EFFICACY ENDPOINT

- Change from baseline in peak SOWS scores over time

6.2 SECONDARY EFFICACY ENDPOINTS

- Change from baseline in peak COWS scores over time
- Change from baseline in average COWS scores over time
- Change from baseline in average SOWS scores over time
- Time to dropout after discontinuation of opioid maintenance (in hours, for Days 6-14)
- Percentage of subjects dropping out after discontinuation of opioid maintenance within each treatment group between Days 6-14
- Total ACES score over time

6.3 EXPLORATORY EFFICACY ENDPOINT

- [redacted]

[redacted]S and SOWS scores for each treatment group at Days 1-5 will also be assessed.

6.4 PHARMACOKINETIC ENDPOINTS

PK endpoints will be described in the PK SAP.

7 STATISTICAL ANALYSES

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

7.1 STATISTICAL METHODOLOGY

7.1.1 *SAMPLE SIZE DETERMINATION*

Due to the exploratory nature of this study, BXCL501 effect size estimates remain to be fully understood, along with the interpretation of the degree of difference (i.e., threshold of clinical importance) between dose conditions (respectively). [redacted]

7.1.2 *POPULATIONS FOR STATISTICAL ANALYSIS*

The following are analysis populations for the study:

- Safety Population (SP): All subjects who receive study drug
- Full Analysis Set (FAS) Population: All subjects who were randomized and treated according to the planned treatment group
- Per Protocol (PP) Population: All subjects in the FAS Population with no major protocol deviations

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.

All data will be provided in listings.

7.1.4 *PROCEDURES FOR HANDLING MISSING DATA*

Approaches for handling missing data will be considered based on the extent of missing data and the reason(s) for missingness.

7.2 SCREENING AND BASELINE CHARACTERISTICS

Summary tables will be constructed by treatment for the Safety Population for the following 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 and concomitant medications (Tables 14.1.5.1-14.1.5.2), laboratory examinations (Tables 14.3.5.1.1-14.3.5.3.2), vital signs (Tables 14.3.6.1.1-14.3.6.2.2), and ECG (Tables 14.3.7.1.1-14.3.7.3.1).

Listings will be provided for eligibility criteria violations, demographics, prior and concomitant medications, medical history, and findings from the MINI (Listings 16.2.3-16.2.4.4 and 16.2.16).

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 as well as provided in a listing (Listing 16.2.2).

7.4 STUDY TREATMENT ADMINISTRATION

Study drug administration data will be listed by subject (Listing 16.2.5.1).

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 full analysis set population will be analyzed and will consist of all subjects who were randomized and treated according to the planned treatment group.

7.5.1 *PRIMARY EFFICACY ENDPOINT*

The primary efficacy endpoint is change from baseline in peak SOWS score. The primary time point is Day 7.

A mixed model for repeated measures (MMRM) will be used to assess treatment group differences for change from baseline in peak SOWS score. Change from baseline scores will include all available time points in a single model. Fixed effects will include treatment group, analysis visit, and a treatment-by-visit interaction. Visit will be fit as an effect in the model using the repeated statement in SAS. The Screening and Baseline (Day 6 pre-first dose) scores will be included as continuous covariates. 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*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, FAS and PP populations). Analysis results from this model at time points other than Day 7 are considered secondary. Line graphs will be provided reflecting changes from baseline in peak SOWS score over time (Figures 14.2.1.1-14.2.1.2, FAS and PP populations).

Individual subject scores, including peak and average scores, for the SOWS for all time points will be provided in a listing (Listing 16.2.6.1).

7.5.2 *SECONDARY EFFICACY ENDPOINTS*

All efficacy assessments will be summarized at all available time points over the course of the study. Continuous secondary endpoints will be analyzed as for the primary analysis, as described above, with the exception of the ACES, which will include only unchanged (ie, not change from baseline) scores and will not include baseline as a covariate in the model. Changes from baseline for peak COWS scores, average COWS scores, and average SOWS scores, and unchanged total ACES scores will be provided in Tables 14.2.2.1-14.2.2.4 (FAS population).

Listings will be provided for individual subject scores, to include peaks and averages (Listings 16.2.6.1-16.2.6.3). Line graphs will be provided reflecting changes from baseline over time in peak and average COWS scores, average SOWS score, and total ACES score (Figures 14.2.2.1-14.2.2.4, FAS population).

Time to dropout after discontinuation of morphine maintenance will be analyzed using a Kaplan-Meier Log Rank test (Table 14.2.2.5, FAS population). Kaplan-Meier estimates will also be used to generate survival curves over time in each treatment group (Figure 14.2.2.5). Total numbers of participants dropping out after opioid discontinuation will be presented by day (Days 6-14), and the overall numbers of participants dropping out will be compared between BXCL501 and placebo using Fisher's Exact tests (Table 14.2.2.6, FAS population).

7.5.3 *EXPLORATORY EFFICACY ANALYSES*

[redacted]

7.5.4 *ADDITIONAL ANALYSES*

[redacted]

7.6 SAFETY ANALYSES

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

7.6.1 *ADVERSE EVENTS*

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 23.0) coding system. 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 subjects who report one or more 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.

Subjects reporting AEs on multiple occasions will be counted only once for each preferred term: under the highest severity when summarized by severity and under the closest relationship to Study Medication when summarized by relationship. If a subject reports multiple preferred terms for a system organ class, the subject will be counted only once for that system organ class.

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

- TEAEs by system organ class and preferred term (Table 14.3.1.1)
- TEAEs by severity, system organ class, and preferred term (Table 14.3.1.2)
- TEAEs by relationship to Study Medication (related, not related), system organ class, and preferred term (Table 14.3.1.3)
- Serious adverse events by system organ class and preferred term (Table 14.3.2.1)
- Serious adverse events by relationship to Study Medication, system organ class, and preferred term (Table 14.3.2.2)
- Adverse events resulting in discontinuation of Study Medication by system organ class and preferred term (Table 14.3.2.3)

By-subject listings will be provided for all AEs, including any deaths, serious adverse events, and AEs leading to discontinuation of treatment (Listing 16.2.7.2, Tables 14.3.2.4-14.2.3.5).

7.6.2 *COLUMBIA SUICIDE SEVERITY RATING SCALE*

Individual C-SSRS subject data will be provided in a listing (Listing 16.2.15).

7.6.3 *CLINICAL LABORATORY EVALUATIONS*

Each laboratory value and change from baseline (for BXCL501 treatment phase and when appropriate) will be summarized using descriptive statistics for hematology, blood chemistry and urinalysis for each treatment and all available time points (Tables 14.3.5.1.1-14.3.5.3.2). Individual subject listings will be

provided, including an indication of clinically significant abnormalities (Listing 16.2.8).

7.6.4 *PULSE OXIMETRY*

Pulse oximetry findings will be included in the vital signs listing by subject (Listing 16.2.10).

7.6.5 *PHYSICAL EXAMINATION*

A listing of abnormal physical examination findings will be provided by subject (Listing 16.2.12). Pregnancy, alcohol screening, and drug testing results will be listed (Listing 16.2.13).

7.6.6 *VITAL SIGNS*

Vital signs will be summarized at each time point for each treatment group and study phase, using descriptive statistics (Table 14.3.6.1.1-14.3.6.2.2). For any vital signs measured in triplicate, the median will be used in the descriptive statistics. Change from baseline in vital signs values as well as postural change will also be summarized for the BXCL501 treatment phase. Individual subject 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 6.

7.6.7 *12-LEAD ELECTROCARDIOGRAM*

Descriptive statistics for ECG parameters will be provided at each time point for each treatment group (Tables 14.3.7.1.1-14.3.7.1.2). The change from baseline in ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group for the BXCL501 treatment phase. Frequencies of ECG finding clinical significance (ie, “Normal,” “Abnormal, CS,” “Abnormal, NCS”) will also be provided (Table 14.3.7.2).

Baseline will be defined as the last ECG value obtained before the first dose of Study Medication on Day 6.

Shift tables comparing QTcF intervals from baseline to each post-baseline time point will be provided by treatment group during the BXCL501 treatment phase and the following ranges (Table 14.3.7.3):

<=450 msec

>450 msec to <=480 msec

>480 msec to <=500 msec

>500 msec

Additionally, the change from baseline frequency distributions of the QTcF interval will displayed by treatment group for the BXCL501 treatment phase for the following data cuts (Table 14.3.7.4):

>30 msec increase

>60 msec increase

Individual subject ECG results and findings will be provided in listings (Listings 16.2.11.1-16.2.11.2).

7.6.8 *CONCOMITANT MEDICATIONS*

Concomitant medications, including an indication of any rescue medications, will be summarized (n and %) by ATC class and preferred term (coded by WHO Drug coding dictionary March 2020) for each treatment group (Table 14.1.5.2). Concomitant medications for individual patients will be provided in a listing (Listing 16.2.4.3).

7.6.9 *STUDY MEDICATION EXPOSURE*

Exposure to Study Medication will be measured by the number of doses received and number of days exposed per treatment group (Table 14.1.6); study administration will provided in a listing (Listing 16.2.5.1). Naloxone administration will also be provided in a listing (Listing 16.2.5.2).

7.6.10 *TIMELINE FOLLOWBACK*

A listing of subjects' responses to the TLFB will be provided (Listing 16.2.14).

7.7 BUCCAL ASSESSMENT

A frequency summary will be presented for subjects with signs of local irritation at 30 min post-dose on Days 1, 6, and 12, and prior to discharge on Day 14. These parameters will be presented for each treatment group at each time point (Table 14.4). A listing of subject-level findings for local irritation will be provided (Listing 16.2.7.1).

7.8 PHARMACOKINETIC ANALYSIS

A separate SAP for the PK analyses will be prepared for the study and will be finalized prior to database lock. Data from subjects who participated in the study will be included in the 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.

7.9 INTERIM ANALYSIS

No interim analyses are planned. However, interim blinded or unblinded analyses may be conducted at the discretion of the sponsor for the purpose of making dose escalation decisions.

8 REFERENCES

Gossop M. The development of a short opiate withdrawal scale (SOWS). Addictive Behaviors, 1990;15(5):487-490.

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.

Sobell LC, Sobell MB, Buchan G, Cleland PA, Fedoroff I, Leo GI. The reliability of the Timeline Followback method applied to drug, cigarette, and cannabis use. 1996 Presented at the 30th Annual Meeting of the Association for Advancement of Behavior Therapy. New York, NY.

Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). Journal of Psychoactive Drugs. 2003;35(2):253-259.

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 as deemed necessary without update to the SAP.

Table	Title	Population
T14.1.1	Analysis Populations	
T14.1.2	Subject Disposition	SP
T14.1.3	Demographics	SP
T14.1.4	Medical & Psychiatric History	SP
T14.1.5.1	Prior Medication	SP
T14.1.5.2	Concomitant Medication	SP
T14.1.6	Study Medication Exposure	SP
T14.2.1.1	Change from Baseline in SOWS Peak Score: Treatment Phase	FAS
T14.2.1.2	Change from Baseline in SOWS Peak Score: Treatment Phase	PP
T14.2.2.1	Change from Baseline in COWS Peak Score: Treatment Phase	FAS
T14.2.2.2	Change from Baseline in SOWS Average Score: Treatment Phase	FAS
T14.2.2.3	Change from Baseline in COWS Average Score: Treatment Phase	FAS
T14.2.2.4	ACES Total Score: Treatment Phase	FAS
T14.2.2.5	Time to Dropout After Morphine Discontinuation	FAS
T14.2.2.6	Number of Participants Dropping out After Morphine Discontinuation	FAS
T14.2.3.1.1	Descriptive Statistics for SOWS Peak Score: Morphine Stabilization Phase: All Subjects	FAS
T14.2.3.1.2	Descriptive Statistics for SOWS Peak Score: Morphine Stabilization Phase: Fentanyl Users	FAS
T14.2.3.1.3	Descriptive Statistics for SOWS Peak Score: Morphine Stabilization Phase: Non-Fentanyl Users	FAS
T14.2.3.2.1	Descriptive Statistics for COWS Peak Score: Morphine Stabilization Phase: All Subjects	FAS
T14.2.3.2.2	Descriptive Statistics for COWS Peak Score: Morphine Stabilization Phase: Fentanyl Users	FAS
T14.2.3.2.3	Descriptive Statistics for COWS Peak Score: Morphine Stabilization Phase: Non-Fentanyl Users	FAS
T14.2.3.3.1	Descriptive Statistics for SOWS Average Score: Morphine Stabilization Phase: All Subjects	FAS

Table	Title	Population
T14.2.3.3.2	Descriptive Statistics for SOWS Average Score: Morphine Stabilization Phase: Fentanyl Users	FAS
T14.2.3.3.3	Descriptive Statistics for SOWS Average Score: Morphine Stabilization Phase: Non-Fentanyl Users	FAS
T14.2.3.4.1	Descriptive Statistics for COWS Average Score: Morphine Stabilization Phase: All Subjects	FAS
T14.2.3.4.2	Descriptive Statistics for COWS Average Score: Morphine Stabilization Phase: Fentanyl Users	FAS
T14.2.3.4.3	Descriptive Statistics for COWS Average Score: Morphine Stabilization Phase: Non-Fentanyl Users	FAS
T14.2.3.5.1	Descriptive Statistics for ACES Total Score: Morphine Stabilization Phase: All Subjects	FAS
T14.2.3.5.2	Descriptive Statistics for ACES Total Score: Morphine Stabilization Phase: Fentanyl Users	FAS
T14.2.3.5.3	Descriptive Statistics for ACES Total Score: Morphine Stabilization Phase: Non-Fentanyl Users	FAS
T14.3.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SP
T14.3.1.2	Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term	SP
T14.3.1.3	Treatment-Emergent Adverse Events by Relationship to Study Medication, System Organ Class, and Preferred Term	SP
T14.3.2.1	Serious Adverse Events by System Organ Class and Preferred Term	SP
T14.3.2.2	Serious Adverse Events by Relationship to Study Medication, System Organ Class, and Preferred Term	SP
T14.3.2.3	Adverse Events Leading to Discontinuation	SP
T14.3.2.4	Listing of Serious Adverse Events	SP
T14.3.2.5	Listing of Adverse Events Resulting in Study Withdrawal	SP
T14.3.5.1.1	Summary of Hematology Measurements: Treatment Phase	SP
T14.3.5.1.2	Summary of Hematology Measurements: Morphine Stabilization Phase	SP
T14.3.5.2.1	Summary of Serum Chemistry Measurements: Treatment Phase	SP
T14.3.5.2.2	Summary of Serum Chemistry Measurements: Morphine Stabilization Phase	SP
T14.3.5.3.1	Summary of Urinalysis Measurements: Treatment Phase	SP
T14.3.5.3.2	Summary of Urinalysis Measurements: Morphine Stabilization Phase	SP
T14.3.6.1.1	Summary of Resting Vital Sign Measurements: Treatment Phase	SP

Table	Title	Population
T14.3.6.1.2	Summary of Standing Vital Sign Measurements: Treatment Phase	SP
T14.3.6.2.1	Summary of Resting Vital Sign Measurements: Morphine Stabilization Phase	SP
T14.3.6.2.2	Summary of Standing Vital Sign Measurements: Morphine Stabilization Phase	SP
T14.3.7.1.1	Summary of Electrocardiogram Measurements: Treatment Phase	SP
T14.3.7.1.2	Summary of Electrocardiogram Measurements: Morphine Stabilization Phase	SP
T14.3.7.2	Frequency of Overall Electrocardiogram Findings Based on Clinical Significance: Treatment Phase	SP
T14.3.7.3	Shift Tables of QTcF Intervals from Baseline: Treatment Phase	SP
T14.3.7.4	Change from Baseline QTcF Frequency Distributions : Treatment Phase	SP
T14.4	Buccal Assessment Findings	SP

9.2 LISTINGS

The following listings are to be included in the post-text Appendix 16 of the CSR and may be modified as deemed necessary without update to the SAP.

Listing	Title	Population
L16.2.1.1	Subject Disposition	SP
L16.2.1.2	Analysis Populations	
L16.2.2	Protocol Deviations	SP
L16.2.3	Inclusion Criteria Not Met or Exclusion Criteria Met	SP
L16.2.4.1	Demographics and Baseline Characteristics	SP
L16.2.4.2	Medical & Psychiatric History	SP
L16.2.4.3	Concomitant Medications	SP
L16.2.4.4	Prior Medications	SP
L16.2.5.1	Study Drug Administration	SP
L16.2.5.2	Naloxone Administration	SP
L16.2.6.1	Individual SOWS Scores	FAS
L16.2.6.2	Individual COWS Scores	FAS
L16.2.6.3	Individual ACES Scores	FAS
L16.2.7.1	Buccal Assessment for Local Irritation	SP
L16.2.7.2	Adverse Events	SP
L16.2.8	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	Physical Examinations (Abnormal Findings)	SP
L16.2.13	Drug and Pregnancy Screening Results	SP
L16.2.14	Timeline Followback	SP
L16.2.15	C-SSRS Results	SP
L16.2.16	MINI Results	SP

9.3 FIGURES

The following figures are to be included in Appendix 14 of the CSR and may be modified as deemed necessary without update to the SAP.

F14.2.1.1	Change from Baseline in Peak SOWS Score	FAS
F14.2.1.2	Change from Baseline in Peak SOWS Score	PP
F14.2.2.1	Change from Baseline in Peak COWS Score	FAS
F14.2.2.2	Change from Baseline in Average SOWS Score	FAS
F14.2.2.3	Change from Baseline in Average COWS Score	FAS
F14.2.2.4	Total ACES Score	FAS
F14.2.2.5	Kaplan-Meier Curves for Time to Dropout After Morphine Discontinuation	FAS
F14.2.3	Mean COWS and SOWS Scores Over Time Per Treatment Group, Days 6-12	FAS