A PHASE Ib/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

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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

PROTOCOL NUMBER:	BXCL501-201
STUDY PHASE:	Phase 1b/2
IND NUMBER:	140184
PROTOCOL VERSION:	3.0
ORIGINAL PROTOCOL DATE:	17 December 2019
AMENDMENT 1 DATE	08 May 2020
AMENDMENT 2 DATE	24 Nov 2020
SPONSORED BY:	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 Phone: [redacted]

PROTOCOL APPROVAL

PROTOCOL TITLE:
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

PROTOCOL NUMBER: BXCL501-201

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ORIGINAL PROTOCOL DATE: 17 December 2019
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AMENDMENT 2 DATE 24 Nov 2020
SPONSOR: BioXcel Therapeutics, Inc.
555 Long Wharf Drive
12th Floor
New Haven, CT 06511
U.S.A.

STUDY PRODUCT: BXCL501

Sponsor Approval:

Date: 12/3/20 Signature: [redacted]

1 PROCEDURES IN CASE OF EMERGENCY

Table 1 Sponsor/CRO Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted]	Cognitive Research Corporation (CRC) 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 [redacted]
Clinical Operations Leader	[redacted]	CRC 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 [redacted]
Medical Monitor	[redacted]	CRC 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 [redacted]
24-hour Emergency Contact	[redacted] Secondary Contact: [redacted]	BioXcel Therapeutics, Inc. 555 Long Wharf Drive 12th Floor New Haven, CT 06511 [redacted] CRC 200 Central Ave, Suite 1230 Saint Petersburg, FL 33701 [redacted]

2 INVESTIGATOR AGREEMENT

A PHASE Ib/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

PROTOCOL NUMBER: BXCL501-201

I have read the protocol and agree that it, along with the related Clinical Trial Agreement, contains all the details necessary to carry out the study. I will conduct this study according to the protocol and will complete the study in the time agreed. Potential additions or modifications to the study will be by mutual written agreement between BioXcel Therapeutics, Inc. and me and will be documented and filed, if required, with the Institutional Review Board and the United States Food and Drug Administration.

I will provide copies of the protocol and other pertinent information to all individuals responsible for assisting me in the study.

BioXcel Therapeutics, Inc., Cognitive Research Corporation, and their designees will have access to source documentation from which case reports have been generated.

Investigator

Signature: _____ Date: _____

Investigator

Name (print): _____

3 SYNOPSIS

Name of sponsor/company: BioXcel Therapeutics, Inc.

Name of investigational product: BXCL501

Name of active ingredient: Dexmedetomidine (DEX)

Protocol number: BXCL501-201

Title of study: 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

Estimated number of study center(s): The study will be conducted at up to 4 sites.

Phase of development: 1b/2

Objectives:

Primary objective:

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.

Secondary objectives:

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
- Percentage of subjects dropping out after opioid discontinuation
- Assessment of safety reflected by scores on the Agitation and Calmness Evaluation Scale (ACES) assessment

Exploratory objective:

- Evaluation of pharmacokinetics in subjects undergoing opiate withdrawal

Study Design: This inpatient Phase 1b/2 study will assess the safety, pharmacokinetics, and early signs of efficacy of escalating doses of BXCL501 versus placebo following discontinuation of morphine maintenance. The opioid maintenance phase will be occurring during Study Days 1-5; the randomized BXCL501/placebo phase will occur on Study Days 6-12. The randomized phase will be followed by 2 days of BXCL501-placebo and morphine-placebo treatment for all remaining subjects on days 13-14.

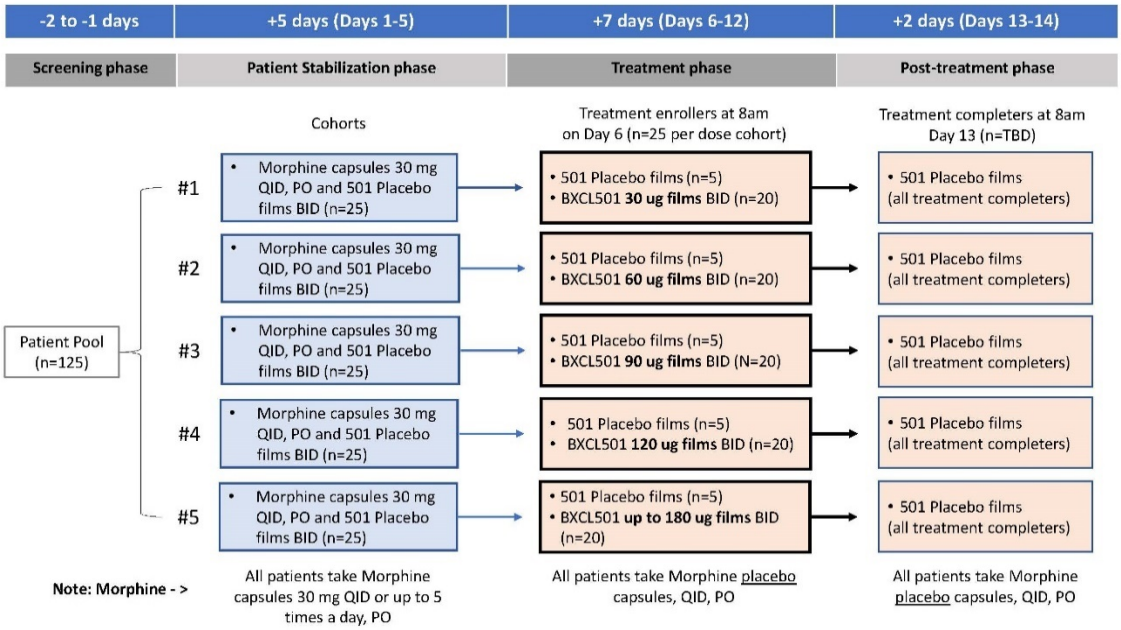
After a 30-day screening period, eligible male and female adult subjects with OUD who are physically dependent on opioids and are not seeking treatment for opioid withdrawal symptoms will be admitted to an inpatient unit. At the start of the opioid maintenance phase (Study Days 1-5), subjects (n=approximately 225 enrollers) will receive oral morphine (30 mg) four times a day (QID) approximately every 4-6 hours or up to 5 times per day as needed. The total dose of morphine during Study Days 1-5 can vary at the discretion of the investigator, between 120-150 mg per day, depending on patients abuse history and need for a higher dose to stabilize withdrawal symptoms. In addition, all subjects will receive placebo films, approximately 12 hours apart during this opioid maintenance phase (i.e., Days 1-5) to simulate and thus blind treatment with BXCL501 during Days 6-12.

Starting on the morning of Day 6, a blinded abrupt discontinuation of active morphine will begin by replacing active morphine with placebo morphine. Placebo morphine capsules will be identical in appearance to the morphine capsules taken during the opioid maintenance period. On this day (Study Day 6), subjects will be randomized to receive either placebo or BXCL501 films administered twice a day (BID), approximately 12 hours apart at approximately 8am and 8pm. BXCL501-placebo or BXCL501 will be administered on Days 6-12 along with placebo morphine (QID). On days 13 and 14, all remaining subjects will receive placebo morphine capsules (QID) and BXCL501 placebo films (BID).

It is anticipated that approximately 9 cohorts will be tested (n=25 per cohort) with potential to add cohorts or select different doses/schedule of dosing based on ongoing safety review and medical monitoring. 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). Doses for cohorts 6-9 will be determined from data acquired from cohorts 1-5. 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. Dropouts after Day 6 will not be replaced. 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 Predose, 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 patients leaving the unit.

The following table is representative of cohorts 1-5 only:



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

Vital Signs, SOWS-Gossop, COWS, pulse oximetry and electrocardiogram (ECG) with rhythm strip will be measured as per the schedule of assessments (Table 2). BXCL or placebo will be

self-administered sublingually under staff observation and subjects will be allowed fluids as desired 15 minutes after completion of dosing. Safety and tolerability assessments will be continued until the morning of Day 14 (day of discharge).

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**.**

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

1. Male and female subjects who are 18 years of age to less than 65 years of age.
2. Meets criteria for moderate to severe opioid use disorder as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by the Mini-International Neuropsychiatric Interview (MINI) with physiological dependence as evidenced by a Clinical Opiate Withdrawal (COWS) score of >5 or a positive naloxone challenge upon admission on Day 1.
3. Subjects who can read, understand and provide written informed consent.
4. Women of childbearing potential must have a negative pregnancy test and agree to be abstinent or use an acceptable method of contraception for the duration of the study.

Exclusion Criteria

1. Positive urine pregnancy test at screening or when tested or currently breast feeding.
2. Clinically significant history of cardiac disease, screening and baseline heart rate of <55 beats per minutes or systolic blood pressure <110 mmHg or diastolic blood pressure <70 mmHg.
3. History or presence of a significant medical disease or disorder which, in the opinion of the investigator, increases the risk or may confound the interpretation of study measures, as confirmed by screening laboratory results.
4. Hepatic dysfunction (marked by ascites, or bilirubin >10% above the upper limit of normal [ULN] or liver function tests >3 x ULN) at the screening visit.
5. Acute active Hepatitis B or C as evidenced by positive serology and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2 x ULN.
6. Clinically significant abnormal ECG findings such as second- or third-degree heart block, uncontrolled arrhythmia, or QTcF (Fridericia correction formula) interval >450 msec for males, and >470 msec for females at screening or prior to dosing.
7. Any psychiatric disorder that would compromise ability to complete study requirements.
8. Currently meets DSM-5 criteria for substance abuse disorder, moderate or severe for any substance other than opioids, caffeine, or nicotine and/or current physical dependence on drugs that pose risk of withdrawal that requires medical management such as alcohol or benzodiazepines.
9. History of suicidal behavior within the last 1 year prior to screening.
10. Participation in a clinical trial of a non-FDA-approved pharmacological agent within 30 days prior to screening.
11. Use of any excluded medication at screening or anticipated/required use during the study period.
12. Subjects with a history of intolerance to morphine.
13. Any finding that, in the view of the principal investigator, would compromise the subject's ability to fulfill the protocol visit schedule or visit requirements.

Test Product, Dose, and Mode of Administration:

BXCL501 30 µg, 60 µg, 90 µg, 120 µg and 180 µg doses will be used for cohorts 1-5 and have been developed as a thin film formulation of DEX for sublingual (SL) administration. The product is a small, solid-dose film formulation designed to completely dissolve in the SL space within 1-3 minutes. Doses for cohorts 6-9 were formulated in the same manner; however, doses for cohorts 6-9 will be determined from data acquired from cohorts 1-5.

Reference therapy, dosage and mode of Administration: Matching placebo films to be taken sublingually as described above.

Duration of Treatment: 30 mg QID or 5x/day Morphine and BXCL501-placebo: 5 days;
BID BXCL501 or BXCL501-placebo and morphine placebo: 7 days;
BXCL501-placebo and morphine placebo: 2 days

Criteria for Evaluation:

Efficacy assessment: Determine the preliminary efficacy of sublingual dosing of BXCL501 in the target population compared to placebo, as measured by improved peak SOWS-Gossop scores.

Safety and tolerability assessments: COWS, SOWS-Gossop, adverse events (AEs), clinical laboratory tests, ECG with rhythm strip, pulse oximetry and vital signs will be monitored for tolerability assessment. The ACES assessment will also be administered as a safety measure. All observed and volunteered AEs will be recorded. The relationship of AEs to the study drugs will be graded as not related, unlikely/remotely related, possibly related, probably related or definitely related by the investigators. Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), orthostatic blood pressure, heart rate, and oxygen saturation will be measured daily throughout the study. The application site of the SL preparation (buccal mucosa) will be inspected for any signs of local irritation.

Additional Assessments:

- Demographic Data
- Medical and Psychiatric History
- Prior and Concomitant Medication
- Physical Examination
- Suicidality
- Pregnancy

Statistical Analysis:

Primary Outcome: Safety and tolerability of ascending doses of BXCL501 in subjects with OUD who are physically dependent on opioids.

Secondary Outcomes:

1) Peak SOWS-Gossop score during Days 6-14.
2) Peak COWS score during Days 6-14
3) Average COWS scores per day for Days 6-14 (an average will be calculated for each day in order to assess time course of withdrawal symptoms).
4) Average SOWS-Gossop scores per day on Days 6-14.
5) Time to dropout after discontinuation of morphine maintenance (Days 6-14).
6) Percentage of subjects dropping out after discontinuation of opioid maintenance within each treatment group between Days 6-14

7) Overall agitation and sedation will be evaluated with the ACES.

General

Data will be summarized by treatment using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and summarized by treatment using frequencies and percentages for categorical variables. Formal statistical tests (when performed) will be 2-sided and tested at the alpha=0.05 level of significance, with 95% confidence intervals provided where appropriate.

Efficacy Analyses

Primary: After the morphine maintenance phase, treatment differences between BXCL501 and placebo on peak SOWS-Gossop scores on Days 6-14 will be analyzed using linear regression or Mixed Model Repeated Measures [MMRM].

Secondary: Peak COWS scores during Days 6-14 will each be compared between the BXCL501 and placebo groups using linear regression or MMRM. Time to dropout after discontinuation of morphine maintenance will be analyzed using a Cox proportional-hazards model. Kaplan-Meier estimates will also be used to generate survival curves over time in each treatment group. Logistic regression model will be used to compare the BXCL501 and placebo groups on the numbers of subjects dropping out after opioid discontinuation.

Safety Analyses

Safety data analyses will be conducted on all subjects receiving at least 1 dose of study drug. The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment, relationship to study drug, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Listings of subjects who withdraw from the study due to an AE, serious AEs and/or death or lack of treatment effect will be presented. Laboratory parameters will be summarized by treatment using descriptive statistics and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics. Chi-square (or Fisher's exact) tests will be used to compare the frequencies of AEs or serious AEs on blood pressure, heart rate, or respiratory drive between BXCL501 and placebo, at the beginning of Day 6 and then daily during the remainder of this study.

Sample Size Determination

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

Table 2 Schedule of Visits and Assessments (BXCL501-201)

		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
12 – Lead ECG[4]	X	X	X	X	X	
Physical Exam[5]	X	X		X	X	
Safety labs	X		X			X
Vital Signs Measurements[6]	X	X	X	X	X	X
HIV Testing	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
Urinalysis	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	X	X	
Administration of Morphine Placebo[14]			X	X	X	

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

Notes:

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5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ACES	Agitation and Calmness Evaluation Scale
AUC	area under the concentration-time curve
BAL	breath alcohol level
BID	twice a day
COWS	Clinical Opiate Withdrawal Scale
C_{max}	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
DBP	Diastolic blood pressure
Dex or DEX	Dexmedetomidine
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRB	Institutional Review Board
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MINI	Mini-International Neuropsychiatric Interview
mL	milliliter
mm	millimeters
mmHg	millimeters of mercury
OUD	Opioid Use Disorder
PEC	Positive and Negative Syndrome Scale – Excited Component
PK	Pharmacokinetic

Abbreviation	Definition
PP	Per Protocol
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
TEAE	treatment-emergent adverse event
TLFB	Timeline Followback
ULN	upper limit of normal

6 INTRODUCTION

6.1 Background and Rationale

Dependence on opioid drugs is a major health and social issue in most societies. Almost 1/3rd of U.S. adults reported use of prescription opioids on the 2015 National Survey on Drug Use and Health (Han et al., 2017). In the 2015 Survey, researchers interviewed over 50,000 adults about their use of opioids in the past 12 months. Based on these results, researchers estimated the following for civilian noninstitutionalized adults: 38% (equivalent to 92 million Americans) had used prescription opioids in the past year, 5% (12 million) misused opioids, and approximately 1% or 2 million Americans have an opioid use disorder (OUD). According to the Centers for Disease Control and Prevention, opioid overdose deaths rose from 8,048 in 1999 to 47,600 in 2017 (Scholl et al., 2019). The effects of the opioid crisis are cumulative and costly for our society—an estimated $504 billion a year in 2015—placing burdens on families, workplaces, the health care system, states, and communities (Office of the Surgeon General, 2018). The opioid crisis is being driven by three trends: 1) an increase in prescription opioid overdose deaths since 1999; 2) the four-fold increase in heroin overdoses since 2010; and (3) the tripling death rate for synthetic opioids like fentanyl since 2013. As a result, the number of people dying from opioid overdoses has increased dramatically (Rudd et al., 2016).

Treatment is central to the reduction of the harms incurred by individuals and the community from opioid use disorder. Managed withdrawal, or detoxification, by itself is not an effective treatment for opioid use disorder (Lipton and Maranda, 1983; Mattick and Hall, 1996). Rates of completion of withdrawal tend to be low, and rates of relapse to opioid use following detoxification are high (Broers et al, 2000; Gossop et al, 1989; Vaillant, 1988). However, withdrawal remains a required first step for many forms of longer-term treatment such as residential rehabilitation and naltrexone maintenance (Kleber and Riordan, 1982). It may also represent the endpoint of an extensive period of substitution treatment such as methadone maintenance. As such, the availability of managed withdrawal is essential to an effective and comprehensive treatment system.

A major challenge to seeking treatment for opioid use disorder is the withdrawal symptoms associated with cessation of opioid drug use. The signs and symptoms of the opioid withdrawal syndrome include irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhea, yawning, lacrimation, sweating, sneezing, rhinorrhea, general weakness, and insomnia. Symptoms of the opioid withdrawal syndrome usually begin two to three half-lives after the last opioid dose, that is six to 12 hours for short half-life opioids such as heroin and morphine, and 36 to 48 hours for long half-life opioids such as methadone. Following cessation of a short half-life opioid, symptoms reach peak intensity within two to four days, with most of the obvious physical withdrawal signs no longer observable after seven to 14 days. As with the onset of withdrawal, the duration also varies with the half-life of the opioid used, and the duration of regular use (Tetrault and O'Connor, 2009). The opioid withdrawal syndrome is rarely life-threatening or associated with significant aberrations of mental state (Farrell, 1994), but the combination of uncomfortable symptoms and intense craving makes completion of withdrawal difficult for most people (Mattick and Hall, 1996; Tetrault and O'Connor, 2009.

The current gold standard of treatment involves gradual reduction of the opioid drug dosage (tapering). The most effective withdrawal method is substituting and tapering with methadone or buprenorphine. This approach derived from observations that the withdrawal syndrome from methadone was milder, though longer, than that from morphine. Methadone's high oral bioavailability, efficacy, and long duration of withdrawal relief (24 to 36 hours) were additional factors that have contributed to it being the main medication used in specialist withdrawal programs since the 1980s. Buprenorphine is also used clinically to taper patients from opioids. However, because buprenorphine is a partial opioid agonist, use of this medication during detoxification requires careful transition from short-acting opioids, such as heroin, because buprenorphine itself can precipitate opioid withdrawal symptoms. A non-opioid medication to facilitate withdrawal suppression from opioid discontinuation in OUD would be of great value.

Discovery of the capacity of the alpha-2-adrenergic agonist clonidine to ameliorate some signs and symptoms of withdrawal led to widespread use of this drug as a non-opioid alternative for managing withdrawal (Gossop, 1988). A recent report also indicated that the signs and symptoms of withdrawal occur and resolve earlier with treatment with an alpha-2-adrenergic agonist compared to methadone withdrawal treatment (Gowing et al., 2002). One mechanism underlying opioid withdrawal is noradrenergic hyperactivity (Gold and Pottash, 1989). The alpha-2-adrenergic agonists act centrally to moderate the symptoms of noradrenergic hyperactivity. In 1978, several groups reported early successful experience with the use of the alpha-2-adrenergic agonist clonidine to treat symptoms of opioid withdrawal (Maze et al., 1988), which has led to the widespread use of medications with this pharmacological mechanism to treat symptoms of withdrawal. Physical dependence and withdrawal are mediated at least in part by the interaction of mu-opioid receptors with neurons that contain the neurotransmitter norepinephrine. Activation of mu-opioid receptors normally suppresses the release of norepinephrine from the locus coeruleus. When opioid use is discontinued or blocked, the locus coeruleus releases excess norepinephrine, and this excess norepinephrine causes many of the withdrawal symptoms noted above. By administering an alpha-2-adrenergic agonist, hyperactivity of locus coeruleus neurons can be blocked and withdrawal symptoms reduced.

The alpha-2-adrenergic agonist clonidine is currently used “off label” for the treatment of withdrawal (Gossop, 1988). However, clonidine can produce problematic side effects, such as sedation and hypotension, generally restricting its use in the outpatient setting (Kleber et al., 1985; Preston and Bigelow, 1985). Lofexidine is an alpha-2-adrenergic agonist that is structurally related to clonidine. One advantage of lofexidine over clonidine is that it is believed to have less hypotensive effects than clonidine (Kahn et al., 1997). Lofexidine is currently approved in the US for the mitigation of withdrawal symptoms during discontinuation from use of opioid drugs under the brand name Lucemyra. In a recent clinical trial of lofexidine, only 41.3% of the participants taking lofexidine and 27.4% of patients on placebo completed the trial (Tirado et al., 2018). As a result, Americans seeking treatment for OUD only have an approximately 4 in 10 chance of completing treatment with the only currently available non-opioid medication, lofexidine.

BioXcel Therapeutics is developing BXCL501 (dexmedetomidine on a sublingual film) for [redacted] Dexmedetomidine is a selective and potent agonist of alpha-2-adrenergic receptors. It is currently used as an intravenous anesthetic for its

anxiolytic, sedative, and analgesic properties. Dexmedetomidine has minimal effects on respiration and is a non-opioid, which contributes to its frequent use in the ICU. Patients receiving dexmedetomidine are easier to rouse, more co-operative, and better able to communicate versus patients receiving midazolam or propofol. Furthermore, dexmedetomidine has an acceptable safety profile with limited adverse events such as hypotension, hypertension and bradycardia compared to other alpha-2-adrenergic agents.

Given these advantageous properties of dexmedetomidine that were characterized by intravenous administration of the drug, BioXcel Therapeutics Inc. developed a sublingual film formulation of dexmedetomidine as a treatment for managing opioid withdrawal. Sublingual dexmedetomidine is formulated as BXCL501 and offers an alternative treatment option for reducing opioid withdrawal symptoms in patients undergoing opioid detoxification.

6.2 Non-Clinical Pharmacology

Dexmedetomidine is a highly selective alpha-2-adrenoceptor agonist on presynaptic neurons. The stimulation of these receptors leads to a decrease in norepinephrine release from presynaptic neurons with inhibition of postsynaptic activation, which attenuates central nervous system (CNS) arousal, especially in the locus coeruleus of the brain.

Alpha-2 selectivity is observed in animals following slow intravenous infusion of low and medium doses of dexmedetomidine (10–300 µg/kg). Both alpha-1 and alpha-2 activity is observed following slow intravenous infusion of high doses (≥ 1000 µg/kg) of dexmedetomidine or in association rapid intravenous administration of dexmedetomidine (Precedex US Package Insert, 2016).

Dexmedetomidine exhibits high potency and intrinsic activity at all 3 types of alpha-2-adrenergic receptors, A, B and C. Because all 3 receptors contribute to reducing sympathetic tone that is part of opioid withdrawal symptoms, dexmedetomidine may be an excellent choice of a drug that reduces these symptoms. Dexmedetomidine has also been studied in rats to determine its free brain to free plasma ratio after sublingual dosing. Dexmedetomidine exhibits 1:1 free brain to free plasma levels, indicating it possesses excellent qualities for a CNS drug.

6.3 Clinical Experience and Pharmacokinetics

A single ascending dose study in normal, healthy volunteers was conducted with BXCL501. The primary objective of this study was to determine the pharmacokinetic (PK), safety, and tolerability of the various film strengths of BXCL501 for identification of appropriate film dosage strengths to be carried forward into subsequent clinical trials. The study evaluated 3 doses (10 µg, 20 µg, 40 µg) of BXCL501 film in 4 cohorts of healthy adult male and female participants (n=12 subjects per cohort 2:1 randomization). Single doses up to 40 µg BXCL501 were well-tolerated. In reviewing the safety and tolerability of the 40 µg dose, there were 3 symptomatic subjects reporting dizziness upon standing, who had concomitant intermittent hypotension or bradycardia. There were no deaths or serious treatment-emergent adverse events (TEAEs) reported in the study. No subject was withdrawn due to a TEAE. The most frequent TEAE during the study was somnolence, which was reported with a slightly higher frequency at doses of 20 µg and 40 µg (75% each) compared to the 10 µg dose and placebo (50% each). No subject dosed in this study required hemodynamic interventions for maintaining BP, cardiac

interventions for maintaining heart rate, or respiratory interventions for maintaining oxygen saturation. The results also show that dexmedetomidine is rapidly absorbed following placement of BXCL501, has a short half-life, and exhibits dose proportionality.

Figure 1 [redacted]

[redacted]

OBJECTIVES

The primary objective of the current trial 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.

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
- Percentage of subjects dropping out after opioid discontinuation
- Assessment of safety reflected by scores on the Agitation and Calmness Evaluation Scale (ACES) assessment

Exploratory objective:

- [redacted]

7 STUDY DESIGN

7.1 Overall Study Design and Plan

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 and are not seeking treatment for opioid withdrawal symptoms 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. Approximately 9 cohorts (N=approximately 225) will be tested. In each cohort, approximately 25 subjects, will receive oral morphine. The total dose of morphine during the maintenance phase (Days 1-5) can vary at the discretion of the investigator, between 120 mg and 150 mg per day depending on patients abuse history and need for higher dose to stabilize withdrawal symptoms. 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. Patients 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). Patients 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 9 cohorts will be tested (n=25 per cohort). 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). Doses for cohorts 6-9 will be determined from data acquired from cohorts 1-5. 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. Dropouts after Day 6 will not be replaced. 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 Predose, 2 hours post dose, pre 2nd dose and 2 hours post second dose.

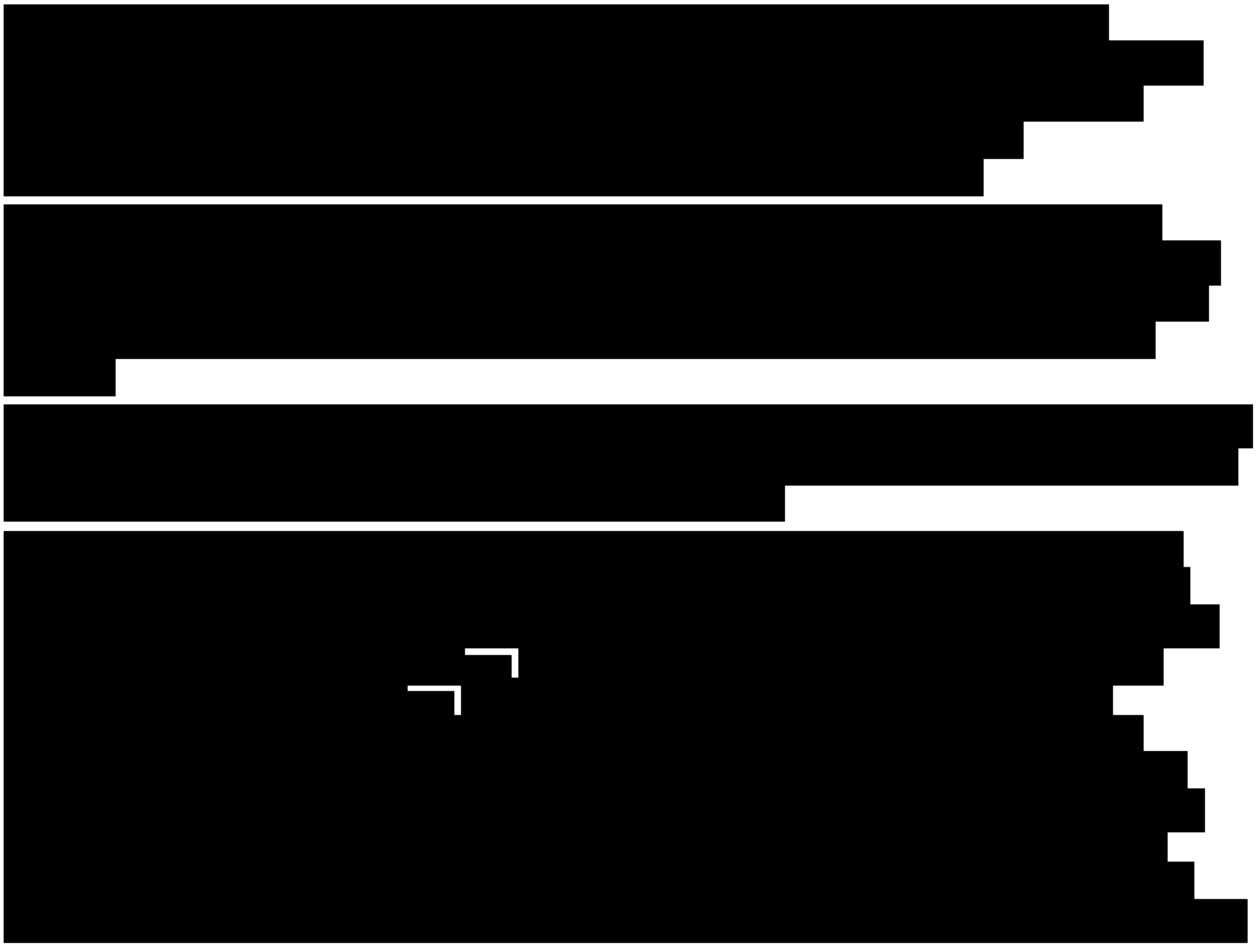
Additional/SOWS-Gossop/COWS may be administered at investigator discretion. Transition to treatment for opioid use disorder will be offered prior to patients leaving the unit.

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.

7.2 Dose Justification



[redacted]

7.3 Study Sites

The study will be conducted at up to 4 sites.

8 SUBJECT POPULATION

8.1 Selection of Study Population

Inclusion Criteria

To be eligible to participate in the study, subjects must meet all of the following criteria:

1. Male and female subjects who are 18 years of age to less than 65 years of age.
2. Meets criteria for moderate to severe opioid use disorder as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by the Mini-International Neuropsychiatric Interview (MINI) with physiological dependence as evidenced by a Clinical Opiate Withdrawal (COWS) score of >5 or a positive naloxone challenge upon admission on Day 1.
3. Subjects who can read, understand and provide written informed consent.
4. Women of childbearing potential must have a negative pregnancy test and agree to be abstinent or use an acceptable method of contraception for the duration of the study.

Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Positive urine pregnancy test at screening or when tested or currently breast feeding.
2. Clinically significant history of cardiac disease, screening and baseline heart rate of <55 beats per minutes or systolic blood pressure <110 mmHg or diastolic blood pressure <70 mmHg.
3. History or presence of a significant medical disease or disorder which, in the opinion of the investigator, increases the risk or may confound the interpretation of study measures, as confirmed by screening laboratory results.
4. Hepatic dysfunction (marked by ascites, or bilirubin >10% above the upper limit of normal [ULN] or liver function tests >3 x ULN) at the screening visit.
5. Acute active Hepatitis B or C as evidenced by positive serology and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2 x ULN.
6. Clinically significant abnormal ECG findings such as second or third degree heart block, uncontrolled arrhythmia, or QTcF (Fridericia correction formula) interval >450 msec for males, and >470 msec for females at screening or prior to dosing.
7. Any psychiatric disorder that would compromise ability to complete study requirements.
8. Currently meets DSM-5 criteria for substance abuse disorder, moderate or severe for any substance other than opioids, caffeine, or nicotine, and/or current physical dependence on drugs that pose risk of withdrawal that requires medical management such as alcohol or benzodiazepines.
9. History of suicidal behavior within the last 1 year prior to screening.

10. Participation in a clinical trial of a non-FDA-approved pharmacological agent within 30 days prior to screening.
11. Use of any excluded medication at screening or anticipated/required use during the study period.
12. Subjects with a history of intolerance to morphine.
13. Any finding that, in the view of the principal investigator, would compromise the subject's ability to fulfill the protocol visit schedule or visit requirements.

8.2 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from participation in this study at any time for any reason and without prejudice.

The investigator may terminate dosing for a subject at any time for any effect that is intolerable to the subject or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or unsuitability for the study in the investigator's opinion to protect the subject's best interest.

If a subject is withdrawn from dosing before completing the study, the reason for withdrawal will be entered on the appropriate Case Report Form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation of dosing.

Subjects who discontinue from the study prematurely after dosing on Day 6 will not be replaced. Subjects who discontinue from the study prior to Day 6 may be replaced at the discretion of the sponsor.

9 STUDY TREATMENTS

9.1 Method of Assigning Subjects to Treatment Groups

Up to 9 cohorts will be tested (n=25 subjects per cohort). Within each cohort, 20 subjects will receive active BXCL501 and 5 subjects will receive placebo. The following doses of BXCL501 will be administered: 30 µg (Cohort 1), 60 µg (cohort 2), 90 µg (Cohort 3), 120 µg (Cohort 4), and 180 µg (Cohort 5). Doses for cohorts 6-9 will be determined based on safety and efficacy data acquired from cohorts 1-5. BXCL501 and BXCL501-placebo kits will be numbered sequentially with treatment allocation randomized to each kit number. Kits will be sent to each site in blocks of 5 or multiples of 5. Only staff who are not involved with the study will be unblinded to the treatment assignments and kit numbers. Site staff will call these unblinded staff who will assign subjects to a kit number in sequential order.

The safety data from the subjects who complete Cohort 1 (BXCL501 30 µg) and subsequent cohorts will be reviewed by the Investigator and the sponsor in a blinded manner on an ongoing basis.

9.2 Identification of Investigational Product

BXCL501 will be provided as a [redacted]

BXCL501 Sublingual dose films and placebo film will be packaged as individual films in a heat-sealed white foil pouch with a drug product label. The pouch has a white colored outer layer with foil colored inner layer.

- 60 µg – green rectangular thin film [redacted]
- 120 µg – green rectangular thin film [redacted]
- 180 µg – green rectangular thin film [redacted]
- Placebo – green rectangular thin film [redacted]

Certain dose strengths will be achieved by cutting films in half to obtain the desired dose.

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

Treatment administration: Subjects will be asked to self-administer the films.

9.3 Identification of Non-investigational Product

Morphine will be provided as an immediate release capsules or tablets (30 mg) formulation.

Treatment administration: As this is an inpatient study, study site personnel will administer the treatments.

9.4 Storage

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

9.5 Labeling

Each container of study drug will be labeled with study specific information that meets all applicable regulatory requirements.

9.6 Drug Accountability

The Investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received study drug. The Investigator will not supply study drug to any person except those named as sub-investigators on the United States Food and Drug Administration Form 1572, designated staff, and subjects in this study. Study drug may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of study drug will be reconciled by the Investigator and returned to the sponsor as directed.

9.7 Blinding and Unblinding Treatment Assignment

This study will be conducted under double-blind conditions so that neither the subject nor the Investigator or study staff members will know the identity of each subject's treatment on days 6-12. BXCL501 film will be provided to the patients for self-administration by a staff member who will not participate in the evaluation of safety or efficacy. Study days 1-5 and 13-14 will be conducted under single-blind conditions where the Investigator, study staff members, and Sponsor will know subject's treatment assignment is BXCL501-placebo film.

Treatment assignment for an individual subject should be unblinded only in an emergency, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The Investigator should contact the medical monitor or project manager before unblinding, when possible, but priority should be given to treatment of the subject. If unblinding occurs without prior approval, the investigator should promptly communicate the circumstances leading to the unblinding by telephone and in writing to the medical monitor.

Breaking of the blind, other than as described above, will be considered a protocol violation. Any subject whose study drug treatment is unblinded will be discontinued and the date, time, and reason for the unblinding must be documented.

9.8 Selection of Dose in the Study

This is a dose ranging study for the treatment of withdrawal symptoms in opioid use disorder. BXCL501 has not been previously tested in this population for the treatment of withdrawal symptoms hence a range of low to moderate/high doses has been chosen. In addition, this dose range has previously been shown to be safe and efficacious in the treatment of agitation in other patient populations.

9.8.1 Treatment Compliance

All unused study medication will be returned the Sponsor. Drug accountability will be performed by study site personnel.

Since treatments will be administered by site staff in this inpatient study, treatment compliance is expected to be 100%.

9.8.2 Concomitant Medications

All concomitant medications used (including over-the-counter medications and herbal and nutritional supplements) will be recorded in the source document and on the appropriate CRF. The medication name, dose, frequency, date, and indication for use must be recorded on the CRF. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator.

9.8.3 Permitted Therapies

Concomitant medications, including prescribed anxiolytics and antidepressants, are allowed (unless specifically prohibited [see Section 9.8.4]) but should be limited to only those medications considered necessary and if the dose is stable at the time of the screening visit and stable throughout the study. Guaifenesin for cough, antacids for indigestion and nausea, Ondansetron (Zofran) for nausea/vomiting, medications for diarrhea, constipation, acetaminophen or ibuprofen for aches and pains.

Lorazepam/clonazepam are permitted provided the subject is not experiencing any somnolence or somnolence-related AEs from investigational product use. To mitigate insomnia, zolpidem will be allowed only if the patient is not experiencing any somnolence or somnolence related AEs from the investigational product use *and* if the zolpidem was not administered within 2 hours of dosing with the investigational product. Zolpidem will only be allowed if determined as necessary by the Investigator.

No clonazepam or any other benzodiazepine will be allowed after day 4 throughout the study except for zolpidem use for insomnia only.

To standardize the use of benzodiazepines, Investigators may prescribe clonazepam on days 1-4 during the morphine stabilization period on the following tapering schedules:

- Day 1: clonazepam 0.5 mg PO Q3-4 hrs. PRN opioid withdrawal (MDD=2 mg)
- Day 2: clonazepam 0.5 mg PO Q3-4 hrs. PRN opioid withdrawal (MDD=1.5 mg)
- Day 3: clonazepam 0.5 mg PO Q3-4 hrs. PRN opioid withdrawal (MDD=1 mg)
- Day 4: clonazepam 0.5 mg PO **once** PRN opioid withdrawal (MDD=0.5 mg)
- Day 5: No clonazepam to avoid potential benzodiazepine withdrawal

Full or partial opioid agonists are permitted for rescue medication purposes only, and if provided, will discontinue the patient from study participation (see Section 9.8.4).

9.8.4 Prohibited Therapies

The following medications are prohibited medications:

Sedative/hypnotics, barbiturates, antihistamines (e.g. diphenhydramine), sedating antidepressants (mirtazapine, trazodone), and triptans (e.g., sumatriptan) unless prescribed and stable prior to admission. Blood pressure lowering drugs and other alpha-2-adrenergic agonists (clonidine,

guanfacine, lofexidine) and alpha-1-adrenergic antagonists (prazosin) are prohibited. Subjects already on antihypertensive medications at study entry may continue on them (provided they are not alpha-2 adrenergic agonists).

If opiate full/partial agonists are required, this will be considered rescue treatment and result in study discontinuation.

10 STUDY PROCEDURES

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

10.1 Screening (within 30 days prior to inpatient admission)

The following procedures and assessments will be performed at Screening:

- Obtain written informed consent. No study procedures may be performed prior to completion of the ICF process.
- Review inclusion and exclusion criteria.
- Collect demographic information.
- Record medical and psychiatric histories, including administration of the Columbia Suicide Severity Rating Scale (C-SSRS) and Mini International Neuropsychiatric Inventory (MINI).
- Record prior and concomitant medications.
- Perform physical examination, including weight and height.
- Record vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- Record a 12-lead ECG.
- Perform rapid urine pregnancy test for all females of childbearing potential and rapid urine pregnancy test on the day of admission to the inpatient unit.
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, HIV, urinalysis, urine drug screen [for opioids, buprenorphine, benzodiazepines, cocaine, amphetamines, and other drugs]), and breath alcohol level (BAL).
- Complete the Timeline Followback (TLFB [i.e., prior use of drug of abuse]) form.
- COWS Assessment
- SOWS Assessment
- Record AEs (after signing the ICF).

The Screening Visit may be conducted over more than one day; however, all procedures must be completed prior to subject randomization and within 30 days of signing informed consent.

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

10.2 Patient Stabilization Phase Study Day 1 (specific assessments on Study Day 1)

The assessments on **Study Day 1** will include:

- SOWS Assessment
- COWS Assessment
- Naloxone challenge (if COWS <6)
- Rapid urine pregnancy testing.
- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- Collect urine samples for clinical laboratory tests (urine drug screen [for opioids, buprenorphine, benzodiazepines, cocaine, amphetamines, and other drugs,]) and breath alcohol level (BAL).
- Physical examination
- 12-lead ECG (pre-morning dose of BXCL501-placebo)
- Record concomitant medication use.
- Assess and record AEs.
- ACES Assessment
- Administration of morphine
- Administration of placebo film
- Buccal Assessment for local irritation

10.3 Patient Stabilization Phase Study Days 2, 3, 4, and 5 (morphine maintenance phase of the study)

The following assessments and procedures performed on all days of the morphine maintenance phase of the study will include:

- Administration of morphine
- Administration of placebo film
- SOWS Assessment
- COWS Assessment
- ACES Assessment
- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- Urine toxicology
- 12 lead ECG (pre-morning dose of BXCL501-placebo)
- Record concomitant medication use.

- Assess and record AEs.

Please note that 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 6-14.

10.4 Randomization Study Day 6

On **Study Day 6**, subjects will no longer receive oral morphine (30 mg). Subjects in each cohort will be randomized to receive either BXCL501 (n=20 subjects) or placebo (n=5 subjects). The assessments and procedures on Study Day 6 will include:

- Review inclusion/exclusion criteria
- Randomization
- SOWS Assessment
- COWS Assessment
- ACES Assessment
- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- 12 Lead ECG (pre-morning dose)
- Record concomitant medication use.
- Assess and record AEs.
- Rapid urine pregnancy testing
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, urine toxicology [for opioids, buprenorphine, benzodiazepines, cocaine, amphetamines, and other drugs])
- Administration of BXCL501 or Placebo film.
- Administration of morphine placebo
- Pharmacokinetics (plasma samples for PK analyses will be collected as listed in the schedule of events – Table 2).
- Buccal Assessment for local irritation

10.5 Treatment Phase Study Days 7-12

On Study **Days 7 to 12**, subjects in each cohort will continue to receive either BXCL501 (n=20) or placebo (n=5). The following assessments and data collected will include:

- SOWS Assessment
- COWS Assessment
- ACES Assessment

- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- Urine toxicology
- 12 Lead ECG (pre-morning dose on Days 8 and 10)
- Physical Examination (Days 8 and 10)
- Record concomitant medication use.
- Assess and record AEs.
- Administration of BXCL501 or Placebo film.
- Administration of morphine placebo
- Pharmacokinetics (plasma samples for PK analyses will be collected as listed in the schedule of events at Day 12 – Table 2).
- Buccal Assessment for local irritation (Day 12)

10.6 Post Treatment Phase or Early Termination Days 13-14

On **Study Days 13-14**, all remaining subjects will receive BXCL501 placebo film and morphine placebo. The following assessments and data collected will include:

- SOWS Assessment
- COWS Assessment
- Record concomitant medication use
- Assess and record AEs
- Physical exam including weight (Day 14/discharge)
- 12 lead ECG (pre-morning dose of BXCL501-placebo)
- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).
- Buccal Assessment for local irritation (Day 14/discharge)
- Administration of BXCL501 placebo and morphine placebo

10.7 Follow-up Period Day 21 *(*1 week after the end of the study*)*

The following assessments and procedures will be conducted 1 week after the end of the study:

- Record concomitant medication use
- Assess and record AEs
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, urine toxicology [for opioids, buprenorphine, benzodiazepines, cocaine, amphetamines, and other drugs]), and breath alcohol level (BAL).
- Vital signs (SBP, DBP, orthostatic blood pressure, pulse rate, and oxygen saturation).

- Timeline Followback

11 STUDY ASSESSMENTS

11.1 Efficacy

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

11.1.1 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 range from 0 to 30, with higher scores indicating greater severity of withdrawal symptoms.

As stated in Section 7.1, SOWS-Gossop is also referred to as SOWS in this document])

A sample of the SOWS form is provided in Appendix B.

11.1.2 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.

The COWS will be administered by an adequately trained professional according to the schedule of events.

A sample of the COWS is provided in Appendix A.

11.2 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.

11.2.1 Sample Collection and Processing

Details of sample processing will be provided in a separate PK manual.

11.2.2 Sample Storage

Plasma samples will be placed in a storage freezer at -70°C (± 12°C) or on dry ice within 120 minutes of the blood collection. Samples will be placed in a -70°C (± 12°C) freezer until they are shipped to the bioanalytical laboratory.

11.2.3 Sample Shipping

- Prior to shipment, the samples will be appropriately packed into a Styrofoam cooler containing dry ice.
- Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 72 hours for remote shipments.
- Samples will be shipped in two aliquots. The second set will be shipped once the status of the first set has been verified.
- The site staff will maintain an inventory of the samples that are to be shipped to the bioanalytical laboratory, including the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. A copy of the inventory will accompany the frozen PK samples.
- The samples will be tracked to ensure arrival in a safe and timely manner.
- Samples will be shipped to:

11.2.4 Analytical Procedures

11.2.4.1 Bioanalytical Sample Analyses

A validated liquid chromatography-tandem mass spectrometry procedure will be used to measure plasma concentrations of dexmedetomidine. Samples from subjects who have at least one post-dose sample will be analyzed.

Analytical results will be presented in tabular form in the final report and chromatographic and derived data will also be provided. Additionally, accuracy, precision, and linearity data for each standard curve and all quality control samples will be presented. Representative chromatograms and standard curve graphs will be included. A bioanalytical sample analysis report with quality assurance statement will be included in the final clinical study report. Copies of serially selected sample chromatograms for 20% of all samples will be included in the final report.

11.2.4.2 Bioanalytical Methodology

The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the appropriate analyte in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

11.3 SAFETY

11.3.1 Adverse Events

11.3.1.1 Adverse Event Definitions

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

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the investigator brochure. For a marketed drug, the known information is in the current package insert.

An unexpected AE is one for which the specificity or severity is not consistent with the current investigator brochure or package insert. For example, hepatic necrosis would be unexpected (greater severity) if the investigator brochure or package insert only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the investigator brochure or package insert only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the medical monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

11.3.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the CRF and reported to the medical monitor. Adverse events will be collected from the time of the first dose of study medication through Day 14 (End of Study) or Early Discontinuation visit and at the one week follow up visit.

AEs will be documented from any data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

11.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dose, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatments or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the MedDRA will be used to code all AEs.

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

The investigator or designee must report any AE that meets the criteria for an SAE (Section 11.3.1.1) to the medical monitor within 24 hours of first becoming aware of the event by telephone. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Investigator information (name, phone, fax, e-mail).
- Protocol number.
- Subject's study identification and initials.
- Subject's date of birth.
- Date of dose of study drug.

- Time and date of occurrence of the event.
- A brief description of the event, outcome to date, and any actions taken.

Within 24 hours of the initial notification, the investigator must e-mail a written SAE report form to the medical monitor/Safety team. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. The investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of the Institutional Review Board (IRB).

The following contact information is to be used for SAE reporting:

BioXcel Therapeutics, Inc. SAE mailbox: [redacted]

11.3.1.3.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

Mild:	Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe:	Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

11.3.1.3.2 Assessment of Relationship

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Not related:	An AE with sufficient evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, and another cause was proven.)
Unlikely/Remotely related:	An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related:	An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related:	An AE with a reasonable time temporal sequence from administration of the study drug; or the AE follows a known pattern of or response to the study drug; or an alternative explanation (e.g. concomitant disease, environment factors, and/or concomitant medications) is less likely than attribution to the study drug; or the AE diminishes or disappears upon cessation of study drug.
Definitely Related:	An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (de-challenge) is clinically reasonable.

11.3.1.3.3 Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as “resolved,” “resolved with sequelae,” “ongoing,” “death,” “other,” or “unknown.”

“Death” should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject’s death, the outcome of death should be indicated for each such AE. Although “death” is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.3.1.4 Follow-up of Adverse Events

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

11.3.2 Laboratory Safety Assessments

- Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Visits and Assessments (Table 2).

Hematology:	Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serology:	HIV
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 Day 21/follow up visit.

11.3.3 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 pre-dose and post-dose 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 <90 mmHg, DBP <60 mmHg, and pulse <60 bpm.

11.3.4 Electrocardiogram

A 12-lead ECG with rhythm strip will be performed at screening, pre-morning dose of BXCL501-placebo on study days 1-5, pre-morning dose on study days 6, 8, 10 and pre-morning dose of BXCL501-placebo on days 13-14/discharge from the inpatient facility.

11.3.5 Physical Examination

A standard physical examination will be performed at screening, study day 1, day 8, day 10, and day 14/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 day 14/discharge.

11.3.6 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 (-5/+15 min) BXCL501 or placebo dosing (approximately 10am and 10pm).

11.3.7 Timeline Follow back

The Timeline Follow back 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.

11.3.8 Concomitant Medications

Concomitant medications will be reviewed and documented during screening, each day during the study, and at the follow up visit.

12 STATISTICAL METHODS

12.1 General Considerations

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

12.2 Analysis Populations

The following analysis populations are planned:

- Safety Population: All subjects who receive study drug.
- Intent to treat (ITT) Population: All subjects in the Safety Population who have a SOWS Score.
- Per Protocol (PP) Population: All subjects in the ITT Population with no major protocol deviations.

12.3 Statistical Analyses

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. Baseline is defined as the last observation prior to initiation of study medication. Missing data will be imputed using Last Observation Carried Forward. Efficacy analyses and summaries will be presented for both the ITT Population and the PP Population, with the former being primary. Details of the statistical analyses will be provided in the SAP, which will be finalized prior to database lock.

12.3.1 Subject Disposition and Demographic Characteristics

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment.

Demographics and baseline characteristics, including age, sex, race, weight, height and body mass index, will be summarized by treatment for the Safety Population.

12.3.2 Efficacy Analyses

12.3.2.1 Primary Efficacy Endpoint

After the morphine maintenance phase, treatment differences between BXCL501 and placebo on peak SOWS scores on Days 6-14 will be analyzed using linear regression or Mixed Model Repeated Measures [MMRM]. Treatment differences between BXCL501 and placebo on peak SOWS scores on Day 7 (two days after opiate discontinuation) as well as peak SOWS on Days 6-14 will be analyzed.

The intent-to-treat population will be analyzed and consist of all patients who take any study medication and who had both baseline and at least 1 efficacy assessment after dosing.

12.3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Peak COWS scores during Study Days 6-14.
- Average COWS scores per day for Days 6-14 (an average will be calculated for each day in order to assess time course of withdrawal symptoms).
- Average SOWS scores per day on Days 6-14
- Time to dropout after discontinuation of opioid maintenance (Days 6-14).
- Percentage of subjects dropping out after discontinuation of opioid maintenance within each treatment group between Days 6-14.
- Overall agitation and sedation will be evaluated with the ACES

Peak COWS scores will be compared between the BXCL501 and placebo groups using linear regression or MMRM. Within each group, COWS and SOWS scores will also be compared on Days 1-5 and Days 6-14.

Time to dropout after discontinuation of morphine maintenance will be analyzed using a Cox proportional-hazards model. Kaplan-Meier estimates will also be used to generate survival curves over time in each treatment group. Logistic regression models will be used to compare the BXCL501 and placebo groups on the numbers of participants dropping out after opioid discontinuation.

12.3.3 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.

The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment, relationship to study drug, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Listings of subjects who withdraw from the study due to an AE, serious AEs and/or death or lack of treatment effect will be presented. Laboratory parameters will be summarized by treatment using descriptive statistics and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics. Chi-square (or Fisher's exact) tests will be used to compare the frequencies of AEs or serious AEs on blood pressure, heart rate, or respiratory drive between BXCL501 and placebo, at the beginning of Day 6 and then daily during the remainder of this study.

12.3.4 Pharmacokinetic Analyses

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.

12.3.5 Interim Analyses

The sponsor is planning to conduct one or more interim analyses to evaluate the safety and efficacy data to help guide the dosing of BXCL501 for future dose cohorts.

12.4 Sample Size Determination

Due to the exploratory nature of this study, BXCL501 effect size estimates remains to be fully understood, along with the interpretation of the degree of difference (i.e., threshold of clinical importance) between dose conditions (respectively). The proposed sample size of approximately 225 participants (25 per dosing cohort, 9 cohorts) should be large enough to obtain at least 10 completers per dosing cohort, ensuring precise 95% confidence intervals on the treatment mean difference with a margin of error of <2.7.

13 STUDY CONDUCT

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

13.1 Sponsor and Investigator Responsibilities

13.1.1 Sponsor Responsibilities

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

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

13.1.2 Investigator Responsibilities

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

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

13.2 Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed consent.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

13.3 Study Documents

All documentation and material provided by the sponsor for this study are to be retained in a secure location and treated as confidential material.

13.3.1 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement).
- Curricula vitae of all investigators and sub-investigators.
- Name and address of the laboratories.
- List of laboratory reference ranges, and if available, a quality certificate.
- Signature Log/Delegation of Study-related Duties.
- United States Food and Drug Administration Form 1572.
- Any other relevant GCP documents.

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

13.3.2 Case Report Forms

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

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

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

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

13.3.3 Source Documents

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

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

Clinical laboratory data required by the protocol will be obtained by local labs. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

13.4 Data Quality Control

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

13.4.1 Monitoring Procedures

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

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

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

By signing the Investigator's Agreement, the investigator agrees to meet with the CRA during study site visits; to ensure that study staff is available to the CRA as needed; to provide the CRA access to all study documentation, to the clinical supplies dispensing and storage area; and to

assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

13.4.2 Data Management

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

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

13.4.3 Quality Assurance/Audit

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

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

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

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

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

13.5 Study Termination

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

13.5.1 Regular Study Termination

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

13.5.2 Premature Study Termination

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

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

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

13.6 Study Site Closure

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

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

13.6.1 Record Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until at least 2 years after the notification of submission of the final study report to regulatory authorities by the sponsor.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After completing the study, the sponsor will be provided with the original CRFs or at least a legible copy and retain the documents at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files, and other source data until at least 5 years after notification of submission of the final study report to the regulatory authorities by the sponsor. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's

notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

13.6.2 Sample Retention

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

13.7 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval by the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency.

13.8 Use of Information

All information about the study drug, the sponsor's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by the sponsor in connection with the continued development of the study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

14 FINAL CLINICAL STUDY REPORT

The final study report will be written according to the "Guideline for Industry (Structure and Content of Clinical Study Reports)" from the International Conference on Harmonisation (ICH) E3. The final study report will present a narrative description of the clinical, analytical, pharmacokinetic, and statistical results. Tables and figures will be "integrated" into the main text, with appendices at the end of the report (e.g., the protocol, sample CRFs, investigator-related information, test/reference product information, subject data listings).

The final clinical study report will be submitted to the appropriate regulatory authorities.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP and the 1996 Version of the Declaration of Helsinki.

15.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent has been obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

15.3 Approval by Institutional Review Board

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

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

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

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17 APPENDICES

APPENDIX A: CLINICAL OPIATE WITHDRAWAL SCALE (SAMPLE)

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

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Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

APPENDIX B: SHORT OPIATE WITHDRAWAL SCALE OF GOSSOP (SAMPLE)

The Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) is a 10-item questionnaire developed to evaluate opioid withdrawal symptom severity. The scale was derived from the original 32-item Opiate Withdrawal Scale in order to reduce redundancy while providing an equally sensitive measure of opioid withdrawal symptom severity appropriate for research and clinical practice. In this document, SOWS-Gossop is also referred to as SOWS.

Table 1.

The Short Opiate Withdrawal Scale.

Please put a check mark in the appropriate box if you have suffered from any of the following conditions in the last 24 hours:

		None	Mild	Moderate	Severe
Feeling Sick	(.47)				
Stomach Cramps	(.60)				
Muscle Spasms/Twitching	(.64)				
Feelings of Coldness	(.62)				
Heart Pounding	(.52)				
Muscular Tension	(.68)				
Aches and Pains	(.63)				
Yawning	(.73)				
Runny Eyes	(.68)				
Insomnia/Problems Sleeping	(.57)				

Note. Table 1 shows the 10 items of the SOWS and the format in which it is administered. The factor loadings as shown with the items do not appear in the SOWS itself.

Table 1 is from Gossop, 1990.

APPENDIX C: AGITATION AND CALMNESS EVALUATION SCALE (SAMPLE)

Rater: _____ Site ID:_____ Subject ID: _____ Date: _____

Agitation-Calmness Evaluation Scale (ACES)

Time conducted _____ (24 hour clock)

Select rating that best describes subject's current status:

- ☐ 1 = Marked agitation
- ☐ 2 = Moderate agitation
- ☐ 3 = Mild agitation
- ☐ 4 = Normal
- ☐ 5 = Mild calmness
- ☐ 6 = Moderate calmness
- ☐ 7 = Marked calmness
- ☐ 8 = Deep sleep
- ☐ 9 = Unarousable