16.1.1. Protocol and Amendments

Summary of Amended Protocol Changes

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 4 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021
Protocol Amendment 2 Date: 03 August 2021
Protocol Amendment 3 Date: 26 October 2021
Protocol Amendment 4 Date: 12 January 2022
Protocol Version: 5.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Covance Study Number: 8463245
IND Number: 134585

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The **primary changes** implemented in this protocol amendment are due to a recent surge in Coronavirus Disease 2019 (COVID-19) cases at one of the clinical sites enrolling subjects in

this study. Between Day -2 and Day 9 there were 21 subjects at the site who tested positive for COVID-19. To protect the safety of the subjects and site personnel, all 35 subjects at the site were discharged from the unit and were discontinued from the study following completion of the Early Termination assessments. Subjects will be monitored as outlined in the protocol.

As a result of this outbreak, the protocol has been modified to allow time for the sites to perform additional COVID-19 tests and confirm results prior to enrolling the subjects in the study. The sites may bring in subjects for check-in on Day -4 rather than Day -2, if necessary. In addition, the number of subjects planned to be randomized in the study was increased from 64 to 68 subjects to ensure an adequate number of evaluable subjects are randomized to meet the objectives of the study.

Minor changes:

1. The protocol version and date were updated throughout the protocol.
2. Typographical errors and formatting errors were corrected, as necessary.
3. List of abbreviations was revised, as necessary.

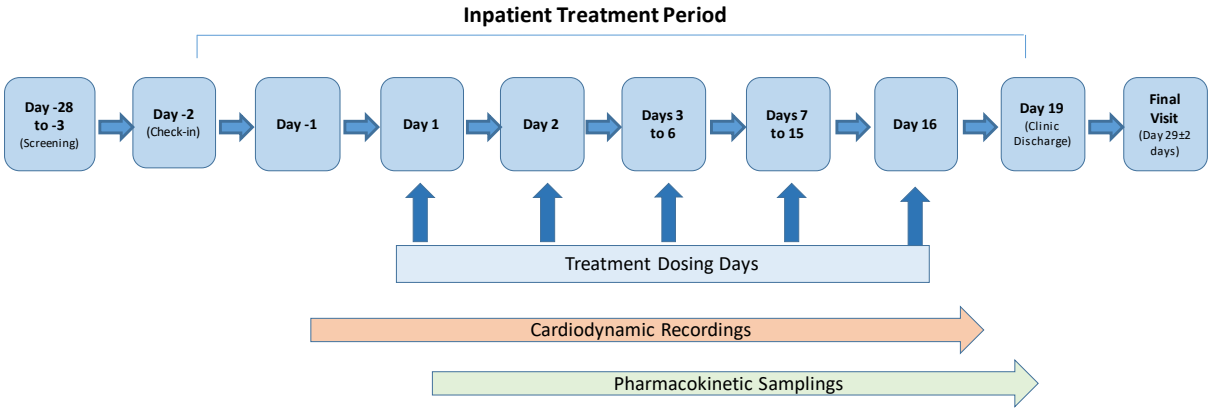
A detailed summary of changes is presented below:

Synopsis and Section 3.1, Overall Study Design paragraphs 3 and 7 (including Figure 1)

Previously read:

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Now reads:

In this study, approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects.

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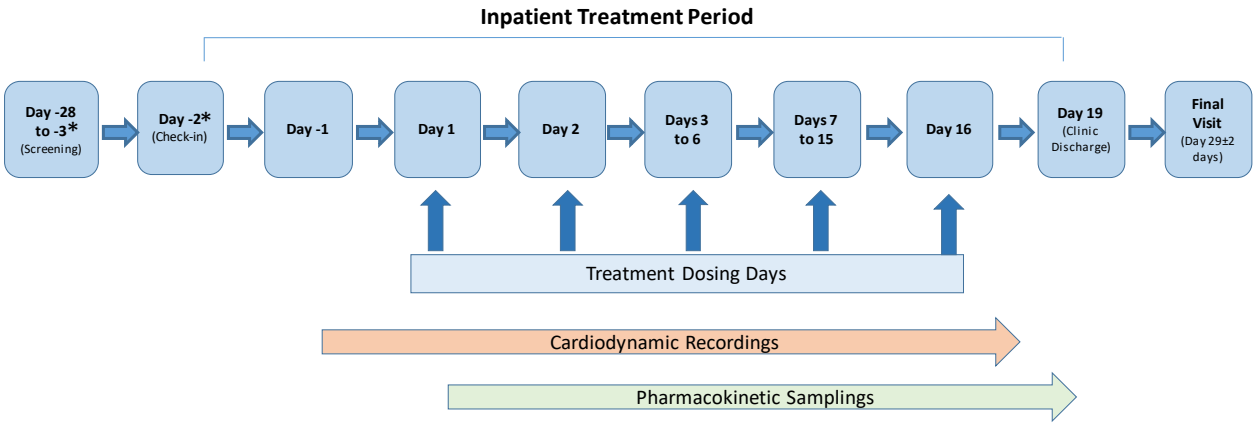

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 (or on Day -4 depending on the clinical site's requirement for Coronavirus Disease 2019 [COVID-19] testing) and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG

timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Section 7, Study Assessments and Procedures

Previously read:

This study includes a screening period (Day -28 to Day -3), a treatment period (Days -2 to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Now reads:

This study includes a screening period (Day -28 to Day -3 [or Day -5 depending on the clinical site's requirement for COVID-19 testing]), a treatment period (Days -2 [or Day -4] to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2 or Day -4 depending on the clinical site's requirement for COVID-19 testing) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Synopsis, Number of Subjects; Section 5.1, Investigational Products; and Section 8.1, Determination of Sample Size

Previously read:

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Now reads:

Approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects.

Appendix 2, Clinical Laboratory Evaluations, Footnote b

Previously read:

[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at Check-in (on Day -2 depending on the clinical site's requirements for

Coronavirus Disease 2019 testing) and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Now reads:

[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at check-in (on Day -4 or Day -2 depending on the clinical site's requirements for Coronavirus Disease 2019 testing) and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 4, Contraception Guidance, last paragraph for female subjects

Previously read:

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2) until 90 days after the follow-up visit.

Now reads:

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2 or Day -4 depending on the clinical site's requirement for COVID-19 testing) until 90 days after the follow-up visit.

Appendix 6, Schedule of Assessments

Previously read:

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X	X				
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.

5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 hour postdose, ±15 minutes for ECGs and vital sign measurements at 2 hours postdose and ±5 minutes for PK sampling at 2 hours postdose, ±5 minutes for 3 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Now reads:

Schedule of Assessments

Study Period	**Screening**	**In-house Treatment Period**												**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3 (or -5 if needed for COVID-19 testing)** [1]	**-2 (or -4 if needed for COVID-19 testing)** [1]	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3 (or -5 if needed for COVID-19 testing)** [1]	**-2 (or -4 if needed for COVID-19 testing)** [1]	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test	X													

Schedule of Assessments

Study Period	Screening	In-house Treatment Period											End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3 (or -5 if needed for COVID-19 testing)** [1]	**-2 (or -4 if needed for COVID-19 testing)** [1]	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
(postmenopausal females only)														
CBP-307/placebo administration			X	X	X	X	X	X	X	X				
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COVID-19 = Coronavirus Disease 2019; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 to 4 days before start of dosing on Day 1 (on Day -4 or Day -2 depending on the clinical site's requirements for COVID-19 testing).
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3. **Screening and Check-in:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
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Protocol

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 4 Status: Final
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Protocol Version: 5.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Labcorp Study Number: 8463245
IND Number: 134585

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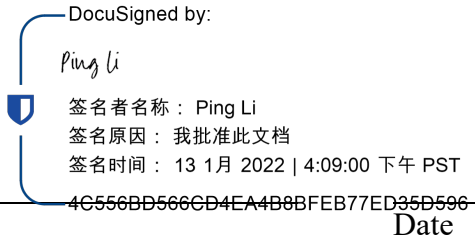
SPONSOR APPROVAL

I have read the protocol and approve it:



Ping Li, MD Date
VP, Clinical Development Asia

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

Nicholas Farinola, MBBS Date
Principal Investigator
CMAX

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

DocuSigned by:
Signer Name: Dr Juan Carlos Rondon
Signing Reason: I approve this document
Signing Time: 13 Jan 2022 | 2:56:23 PM PST
71B57DFEC04E4C8EA1F9D1C490821C54

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SYNOPSIS

Study Title

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the pharmacokinetics (PK) of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on heart rate (HR), PR and QRS intervals, and T-wave morphology.

Study Design

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, multi-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on

Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 (or on Day -4 depending on the clinical site's requirement for Coronavirus Disease 2019 [COVID-19] testing) and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK

sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Number of Subjects

Approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 titrated to 0.1 mg on Day 2; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)

- Moxifloxacin (400 mg; oral tablet).

Duration of Subject Participation in the Study

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3 [or Day -5 depending on the clinical site's requirement for COVID-19 testing]), 21+2 days for the in-house treatment period (Days -2 [or Day -4] to 19), and 10 ±2 days for follow-up (Day 29±2 days), in total approximately 59 days.

Endpoints

Electrocardiogram (Cardiodynamic):

The primary cardiodynamic endpoint is the change-from-baseline QTcF (ΔQTcF).

The secondary cardiodynamic endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);
- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CBP-307. The PK parameters of CBP-307 will be calculated using a model independent approach. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}), and time of the maximum observed concentration (t_{max}). Other noncompartmental parameters may be reported.

Safety:

Adverse events, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12-lead ECGs, and vital signs measurements.

Statistical Methods

Cardiodynamic evaluation:

The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of CBP-307 and change-from-baseline QTcF (ΔQTcF) with

the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma levels. Placebo-corrected ΔHR, ΔPR, ΔQRS, and ΔQTcF (ΔΔHR, ΔΔPR, ΔΔQRS, and ΔΔQTcF) will also be evaluated at each postdosing timepoint ('by-timepoint' analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.

Pharmacokinetics:

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by cohort. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

Pharmacokinetic/electrocardiography analyses:

The relationship between CBP-307 plasma concentrations and the change from ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CYP	cytochrome P450
Δ	change-from-baseline
ΔΔ	placebo-corrected or placebo-adjusted change-from-baseline
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HR	heart rate
HREC	human resource ethics committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
IRB	institutional review board
LOESS	locally estimated scatterplot smoothing
LS	least squares
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
QD	once daily
QTc	heart-corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method

SAE	serious adverse event
SD	standard deviation
SE	standard error
S1P1	sphingosine-1-phosphate receptor 1
TEAE	treatment-emergent adverse event(s)
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
TQT	thorough QT
V_z/F	apparent volume of distribution
WBC	white blood cell
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the investigator's brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Disease Background

Autoimmune diseases are serious disorders that afflict a large portion of the world population; most have no cures. Significant advances have been made in the development of novel and disease-modifying therapies, but many of these new treatments have significant side effects. Treatments are needed that provide better risk-to-benefit profiles than the existing therapeutic choices.

T cells are important immune cells that mediate the development of autoimmune disorders. Migration of T cells from lymphoid tissues to the sites of inflammation is central to the functions of T cells, and this process is dependent on sphingosine-1-phosphate (S1P) receptor 1 (S1P1) which is known to ameliorate a variety of autoimmune diseases in animals and humans. Down modulation of this receptor, using S1P1 agonists, prevents T cell egress and results in a reduced number of circulating lymphocytes, particularly the CD4+- and CD8+-naïve and central-memory T cell subsets.

1.2. Overview of CBP-307

CBP-307 is an S1P1 agonist that is being developed as a treatment for autoimmune diseases by Suzhou Connect Biopharmaceuticals, Ltd. CBP-307 (1-(2-fluoro-4-(5-(4-isobutylphenyl)-1,2,4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid hemihydrate) is a potent, selective, small-molecule agonist of S1P1 and S1P5 receptors. Cell-based assays have confirmed CBP-307 induces internalization of S1P1 from the cell surface. This is consistent with the known mechanism of action of other S1P1 agonists, in that they down-modulate S1P1 and inhibit lymphocyte egress from lymphoid tissues.

1.2.1. Summary of Clinical Experience

The Phase 1 development of CBP-307 comprised 2 completed studies in healthy subjects:

- A single and multiple ascending dose study to evaluate the safety and tolerability of CBP-307 including pharmacokinetic (PK), pharmacodynamic (PD), and food-effect assessments (Study CBP-307AU001)
- A single-dose and multiple-dose, and fixed-dose titration study to evaluate the safety and tolerability of CBP-307 including PK and PD (Study CBP-307CN001)

Currently, CBP-307 is being evaluated in 2 Phase 2 studies:

- Ongoing multicenter study in subjects with moderate to severe ulcerative colitis (Study CBP-307CN002) to compare the clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing

achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

- Ongoing study in subjects with moderate to severe Crohn's disease compares clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

1.2.1.1. Safety

Study CBP-307AU001

A total of 44 healthy subjects were enrolled in the study. There were 28 subjects evaluated using the single-dose regimen (0.1, 0.25, 0.5, and 2.5 mg CBP-307) of which 21 subjects received CBP-307 and 7 subjects received placebo. Another 16 healthy subjects were evaluated using the multiple-dose regimen (0.15 and 0.25 mg CBP-307 given once daily [QD] for 28 consecutive days) of which 12 subjects received CBP-307 and 4 subjects received placebo.

Overall, no unexpected safety signals were identified and no deaths occurred in this study. For the single-dose regiment, no subjects were discontinued due to a treatment-emergent AE (TEAE). In the multiple-dose regimen, there were 2 subjects who were discontinued from the study (due to increased alanine transaminase and second degree AV block [not considered to be clinically significant, as judged by the investigator]). All TEAEs resolved by the end of the study.

In the single-dose regimen groups, TEAEs were reported in 12 of 21 subjects (57.1%) treated with CBP-307 and in 3 of 7 subjects (42.8%) treated with placebo. Most (91.7%) of the TEAEs in these subjects were mild in severity. The most common TEAEs in the CBP-307-treated groups were headache (28.6%); dizziness (19.0%); and bradycardia (9.5%). Bradycardia was reported only in 2 subjects receiving the highest (2.5 mg) CBP-307 dose. One subject had a serious adverse event (SAE) of bradycardia (associated with transient asystole) following a single dose of 2.5 mg CBP-307.

In the multiple-dose regimen groups, CBP-307 at doses of 0.15 and 0.25 mg QD was generally well tolerated over the 28 days of dosing. Treatment-emergent AEs were reported in 11 of 12 subjects (91.7%) in the CBP-307 groups and 2 of 4 subjects (50.0%) in the placebo groups. Most (83.3%) TEAEs were mild in severity. The most common TEAEs in the 2 CBP-307 groups were headache (50.0%), and fatigue, nausea, and musculoskeletal pain (16.7% each). The incidences of these TEAEs were similar in both CBP-307-treated groups. No SAEs were reported for subjects in the multiple-dose regimen.

Study CBP-307CN001

A total of 30 eligible subjects completed 3 CBP-307 dose groups in ascending order of dose after randomization (in a ratio of 1:1:1): Group A (0.1 mg), Group B (0.2 mg), and Group C (0.3 mg). Each dose group consisted of 10 subjects, including 8 subjects receiving the investigational drug and 2 subjects receiving placebo by random assignment. The administration started from the dose of 0.1 mg. The subjects in this group received a single

dose of CBP-307 or placebo and were followed up for safety and tolerance within the next 7 days. Then the subjects received 0.1 mg CBP-307 or placebo QD for 14 consecutive days and were followed up for safety and tolerance within the next 7 days. Dose escalation did not occur until the review of the single-dose regimen safety data from the 6 subjects in the previous dose cohort, and the safety data did not meet the termination criteria. The subjects in the dose of 0.3 mg received fixed-dose titration regimen, ie, 0.05 mg CBP-307 or placebo QD for 3 consecutive days; 0.1 mg CBP-307 or placebo QD for 2 consecutive days; 0.2 mg CBP-307 or placebo QD for 2 consecutive days; finally, 0.3 mg CBP-307 or placebo QD for 14 consecutive days, and the subjects were followed up for safety and tolerance within the next 7 days.

Overall, no unexpected safety signals were identified, and there were no deaths, SAEs, or AEs leading to the subject's early withdrawal from the study after administration of CBP-307. In the safety set, a total of 29 subjects (8 in Group A, 100%; 8 in Group B, 100%; 8 in Group C, 100% and 5 in placebo group, 83.3%) experienced TEAEs.

During the single-dose period, a total of 14 subjects (5 of 8 in Group A, 62.5%; 6 of 8 in Group B, 75%, and 3 of 4 in placebo group, 75%) developed AEs. The incidence of TEAEs in Group A was generally similar to the placebo group. Among TEAEs in Group B, the incidence of AEs related to abnormalities in investigations was higher than that in placebo group, including lymphocyte count decreased (12.5%), white blood cell (WBC) count decreased (12.5%), neutrophil count decreased (12.5%), alanine aminotransferase increased (25%), and gamma-glutamyltransferase increased (12.5%), and aspartate aminotransferase increased (12.5%). Additionally, 1 subject experienced heart rate (HR) decreased (12.5%).

During dose-titration period, 2 subjects (2 of 8 in Group C, 25%) experienced TEAEs. The TEAEs reported in Group C during the titration period included cough (12.5%) and increased upper airway secretion (12.5%). There were no TEAEs in the placebo group during this period.

During repeated-dose period, a total of 28 subjects (8 of 8 in Group A, 100%; 8 of 8 in Group B, 100%; 8 of 8 in Group C, 100%; and 4 of 6 in placebo group, 66.7%) experienced AEs. The most frequent TEAE in Group A was upper respiratory tract infection (37.5%) compared with placebo group; the most frequent TEAEs in Group B and Group C included decreased lymphocyte count (Group B, 87.5%; Group C, 100.0%), WBC count (Group B, 87.5%; Group C, 62.5%), and neutrophil count (Group B, 50%; Group C, 12.5%). The TEAEs noted in Group B during the repeated-dose period also included increased alanine aminotransferase (25%), gamma-glutamyltransferase (37.5%), and aspartate aminotransferase (12.5%), upper respiratory tract infection (12.5%), influenza (12.5%), chest pain (12.5%), lethargy (25%), and neck pain (12.5%); TEAEs in Group C during the repeated-dose period also included increased alanine aminotransferase (25%), decreased HR (12.5%), and mouth ulcer (12.5%); the TEAEs in placebo group included increased transaminase (16.7%), prolonged activated partial thromboplastin time (1/6, 16.7%), decreased hemoglobin (16.7%), upper respiratory tract infection (16.7%), diarrhea (16.7%), dizziness (16.7%), and palpitations (16.7%).

Study CBP-307CN002

This study is ongoing and there are no safety data available.

Study CBP-307CN003

This study is ongoing and there are no safety data available.

1.2.1.2. Pharmacokinetics

CBP-307 given orally as a single dose was readily absorbed; drug concentrations peaked at approximately 6 hours after administration, with an elimination apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours (range of 23 to 29 hours). The time to maximum observed concentration (C_{max}) in the blood was delayed from 6 hours to approximately 10 hours when CBP-307 was given with a high-fat diet. Food consumption also increased exposure (Table 1).

For the single-dose administration, CBP-307 exposure (based on C_{max} and area under the concentration-time curve [AUCs]) increased with increasing dose following a single-dose administration (Table 1).

Table 1: Pharmacokinetics Parameters in the Single-Dose CBP-307 Regimen (Study CBP-307AU001)

Single-Dose Regimen PK Parameters	Mean CBP-307 Single Dose ± SEM (n)				
	0.1 mg	**0.25 mg**	**0.5 mg (fasted)**	**0.5 mg (fed)[a]**	**2.5 mg**
AUC_{last} (ng*h/mL)	13.4 ± 3.54 (n = 6)	45.1 ± 5.25 (n = 6)	160 ± 22.8 (n = 6)	290 ± 28.1 (n = 6)	550 ± 96.3 (n = 3)
AUC_{inf} (ng*h/mL)	ND	63.7 ± 2.14 (n = 3)	214 ± 58.3 (n = 3)	355 ± 44.3 (n = 5)	710 ± 164 (n = 2)
C_{max} (ng/mL)	0.537 ± 0.0931 (n = 6)	1.53 ± 0.0935 (n = 6)	4.84 ± 0.706 (n = 6)	8.58 ± 1.11 (n = 6)	19.0 ± 3.55 (n = 3)
t_{max} (hours)	7.33 ± 1.33 (n = 6)	5.33 ± 0.99 (n = 6)	5.00 ± 0.86 (n = 6)	10.67 ± 2.72 (n = 6)	6.00 ± 2.00 (n = 3)
$t_{1/2}$ (hours)	ND	23.3 ± 1.70 (n = 3)	28.8 ± 1.28 (n = 3)	26.0 ± 1.17 (n = 5)	22.8 ± 3.96 (n = 2)

Abbreviations: AUC_{inf} = area under the curve at infinity; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; h = hour(s); mg = milligram(s); ND = not determinable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SEM = standard error of the mean; $T_{1/2}$ = elimination half-life; t_{max} = time to maximum concentration.
[a] Study Part 1b: Cohort 3 from Part 1a returned to receive a single oral dose of CBP-307 at 0.5 mg under fed conditions.
Source: Final report for Study CBP-307AU001.

For the repeated-dose administration of CBP-307, the C_{max} and AUCs increased with the higher administered dose (Table 2). At the steady-state timepoint on Day 28, the median CBP-307 t_{max} was 4 to 6 hours. The average $t_{1/2}$ was similar, ranging 44 to 49 hours, and there were no dose-dependent changes in $t_{1/2}$ within the dose range. The $t_{1/2}$ was slightly prolonged after repeated-dose administration when compared with that after a single-dose administration. Moderate accumulation of CBP-307 (approximately 3 times the levels

following a single dose) was noted in plasma after QD administration for 14 consecutive days.

Table 2: Pharmacokinetics Parameters in the Multiple-Dose CBP-307 Regimen (Study CBP-307AU001)

Multiple-Dose Regimen PK Parameters	Multiple-Dose Cohort 1 CBP-307 Dosing, mg (± SD) (n)		Multiple-Dose Cohort 2 CBP-307 Dosing, mg (± SD) (n)	
	Day 1 0.1	Day 28 0.25	Day 1 0.15	Day 28 0.15
AUC_{0-24} (ng*h/mL)	24.5 ± 3.26 (n = 5)	125 ± 12.4 (n = 4)	26.3 ± 7.45 (n = 5)	79.7 ± 27.3 (n = 6)
AUC_{last} (ng*h/mL)	NA	203 ± 21.9 (n = 4)	NA	131 ± 44.7 (n = 6)
C_{max} (ng/mL)	1.45 ± 0.214 (n = 5)	6.30 ± 0.588 (n = 4)	1.32 ± 0.422 (n = 6)	4.23 ± 1.45 (n = 6)
t_{max} (hours)	6.80 ± 1.50 (n = 5)	6.50 ± 1.50 (n = 4)	5.00 ± 0.68 (n = 6)	4.33 ± 0.33 (n = 6)

Abbreviations: AUC_{0-24} = area under the curve from time 0 to 24 hours; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; mg = milligram(s); NA = not applicable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SD = standard deviation; t_{max} = time to maximum concentration.
Source: Final report for Study CBP-307AU001.

1.3. Overview of Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of International Council for/Conference on Harmonisation (ICH) E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[2]

1.4. Study Rationale

Regulatory guidance (ICH E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase 1, 2, and 3 trials may be conducted they usually have an insufficient sample size, infrequent sampling of ECG data, or the use of inadequate controls to overcome the high rate of spontaneous change in QTc duration. This has resulted in regulatory guidance recommending a dedicated or thorough trial to define the ECG effects of new drugs.

This study will be done in healthy subjects to eliminate variables (concomitant drugs, diseases, etc.) known to have an effect on ECG parameters. A supratherapeutic dose of CBP-307 is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (eg, concomitant use of cytochrome P450

[CYP]3A4 inhibitor, concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to allow for PK to QTc modeling to assess the effect of drug concentration on cardiac repolarization.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with CBP-307 may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the PK of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on HR, PR and QRS intervals, and T-wave morphology.

2.2. Endpoints

2.2.1. Electrocardiogram Endpoints

2.2.1.1. Primary

The primary endpoint is the change-from-baseline QTcF (ΔQTcF).

2.2.1.2. Secondary

The secondary endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);

- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

2.2.2. Pharmacokinetic Endpoints

Pharmacokinetic parameters of CBP-307 will be determined if data allows:

- area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf})
- area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})

Other PK parameters may also be reported.

2.2.3. Safety Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, multi-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether

volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

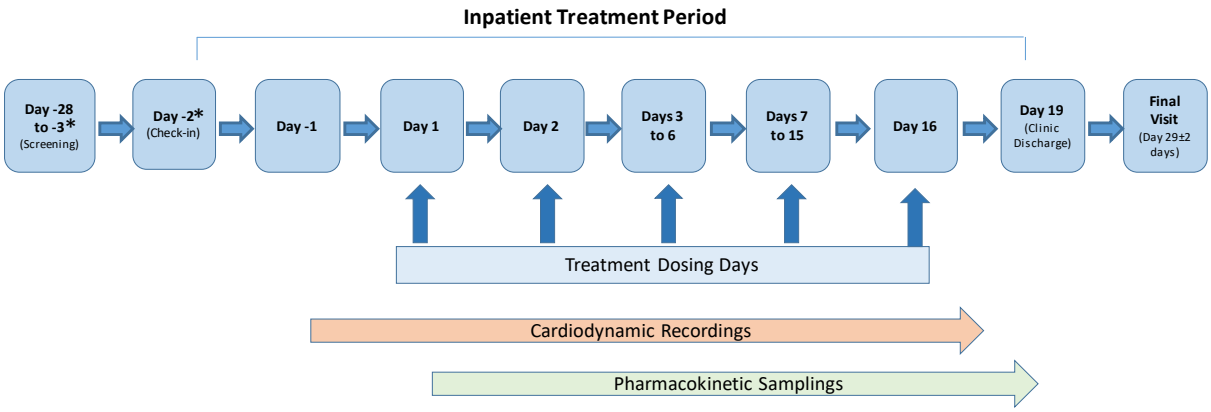
The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



*Subjects will be asked to arrive at the clinical site in the afternoon 2 to 4 days before start of dosing on Day 1 (on Day -4 or Day -2 depending on the clinical site's requirements for Coronavirus Disease 2019 testing). Approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Day 2, Days 3 to 6, Days 7 to 15, and Day 16. Dosing details are provided in Table 3. Blood samples for pharmacokinetic analysis

will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. An end-of-study visit will occur on Day 29±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 (or on Day -4 depending on the clinical site's requirement for Coronavirus Disease 2019 [COVID-19] testing) and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for CBP-307 to cause QT prolongation. As CBP-307 exposure affects heart rate, the primary endpoint for this study will be the QTcF.

The study will be randomized and double-blind because randomization eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions, thus eliminating the possibility that the observed effects of the intervention are because of differential use of other treatments.

The sample size for this study is based on a formal statistical power calculation.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Both male and female subjects will be included to eliminate similar known ECG variability effects.

Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Pharmacokinetic assessments of CBP-307 concentrations in plasma will be evaluated during the study. The timepoints for the PK sample collections are based on previous studies and are considered adequate to allow for the characterization of the drug's PK after oral dosing. Furthermore, the chosen PK sample collection for CBP-307 is anticipated to be sufficient to allow reasonable estimation of $t_{1/2}$ during the terminal elimination phase.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.05 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2 and a dose of 0.2 mg on Days 3 to 6. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at

substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index between 18.0 and 30.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and confirmed at check-in as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4. Negative pregnancy test for females of childbearing potential at screening (blood test) and check-in (urine test).
5. Supine diastolic blood pressure between 60 and 90 mmHg and systolic blood pressure between 90 and 140 mmHg (inclusive) at screening on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest.
6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 55 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.
7. Has serum potassium, calcium, and magnesium levels within the normal reference range at screening, as judged by the investigator.
8. Able to swallow multiple tablets (based on subject's verbal confirmation).
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Subject is mentally or legally incapacitated or has had significant history of recent mental health issues requiring medication and/or hospitalization at the time of the screening visit or expected during the conduct of the study.
2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee). *Note: Childhood asthma that is considered recovered or seasonal allergies that are not currently active or requiring treatment are allowed.*
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
4. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
5. History of significant multiple and/or severe allergies (eg, latex allergy, band-aids, adhesive dressing, or medical tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.
6. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs within 6 months prior to the first dose of study drug (uncomplicated appendectomy and hernia repair will be allowed).
7. History or presence of:
    a. Hypokalemia, in the opinion of the investigator (or designee);
    b. Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
    c. Sick sinus syndrome, second, or third degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities;
    d. Repeated or frequent syncope or vasovagal episodes;
    e. Hypertension, angina, bradycardia, or severe peripheral arterial circulatory disorders.
8. Clinically significant abnormalities (as judged by the investigator in laboratory tests results [out-of-range results confirmed on repeat]), including but not limited to the following parameters:
    a. alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin greater than 1.5 × upper limit of normal;
    b. hemoglobin <10 g/dL, WBC <3.0 $\times 10^9$/L, neutrophils <1.5 $\times 10^9$/L, lymphocytes <0.8 $\times 10^9$/L and platelets <100 $\times 10^9$/L or >1200 $\times$ 10^9/L;

9. History or evidence of alcoholism or drug/chemical abuse within 12 months prior to check-in.
10. Alcohol consumption of >10 units per week for males and females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
11. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.
12. Positive hepatitis panel, positive syphilis test, and/or positive human immunodeficiency virus test (Appendix 2).
13. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 28 days prior to the first dose of study treatment on Day 1. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
14. Participation in a previous clinical study where subjects received CBP-307.
15. Administration of a COVID-19 vaccine in the past 28 days prior to first dose of study treatment on Day 1.
16. Use or intend to use any prescription medications/products within 14 days prior to first dose of study drug (Day 1) and throughout the study, unless deemed acceptable by the investigator (or designee). *Note: For females only, the use hormonal contraception, hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives within 14 days prior to Day 1 is not acceptable, except for Mirena®.*
17. Use or intend to use any drugs known to be significant inhibitors or inducers of CYP enzymes and/or P-gp, including St. John's Wort, for days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the investigator or designee to confirm the lack of PK/PD interaction with the study drug.
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intend to use any nonprescription medications/products including antacids, vitamins (especially those containing magnesium, aluminum, iron, or zinc), minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
21. Has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for whatever reason), in the opinion of the investigator, within the 28 days prior to the first dose of study treatment, and throughout the study.
22. Consumption of caffeine/xanthine-containing foods or beverages within 48 hours prior to check-in until discharge.

23. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
24. Receipt of blood products within 2 months prior to check-in.
25. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
26. Poor peripheral venous access.
27. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Eligible subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). The screening number will be used on all safety samples throughout the study. Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw their informed consent from the study at any time or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, or the inability of the subject to comply with the protocol-required visits or procedures. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- investigator decides to terminate the study due to safety concerns such as AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development
- sponsor requests for termination (eg, due to financial or management reasons, etc.) under the premise to fully protect the safety and rights of subjects
- health authority or institutional review board (IRB)/ethics committee (EC) orders the termination of the trial for any reason.

Definition of end-of-treatment and end-of-study

- end-of-treatment is completion of safety follow-up or withdrawal from the study. End-of-study is the last visit by the last subject.

5. STUDY TREATMENTS

Study treatments are defined as any investigational product (IP), non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as IMP and non-IMP, respectively.

5.1. Investigational Products

The details regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 will be provided in a separate document. Approximately

68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects.

Table 3: Study Treatments

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1		1 capsule		1 tablet
	Group 2A		1 capsule		1 tablet
	Group 2B		1 capsule	1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's	The quantity administered, date administered, and lot number of investigational product is to be recorded on each	The quantity administered, date administered, and lot number of investigational product is to be recorded on each	The quantity administered, date administered, and lot number of investigational product is to be recorded on each

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
		electronic case report form (eCRF).	subject's eCRF.	subject's eCRF.	subject's eCRF.
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

All supplies of the IMP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study treatments will be stored at the study site in a location that is locked with restricted access.

5.2. Study Treatment Administration

Each dose of study treatment (CBP-307, placebo, or moxifloxacin) will be administered orally following an overnight fast of at least 10 hours, with approximately 240 mL of room temperature water. Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Subjects will be dosed in numerical order while sitting or standing but not be permitted to lie supine for 2 hours after treatment administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a double-blind randomized study. Subjects will be randomized to one of the treatment sequences before administration of the first dose of study treatment. A randomization list will be generated by a statistician using a computer-generated pseudo-random permutation procedure. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the study site. Randomization details will be included in the randomization specification.

5.4. Blinding

This is a double-blinded study. The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to CBP-307 or moxifloxacin.
- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.
- Interim bioanalytical data will be provided to Labcorp Early Clinical Biometrics in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing coded details of the treatment. These individually sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until the completion of the study.

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy, per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from the use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the investigator (or designee) and/or sponsor have given their prior consent. Medications taken within 28 days before study treatment administration will be documented as a prior treatment. Treatments taken after study treatment administration will be documented as concomitant treatments.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for the treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Females will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives (with the exception of Mirena®) during the study until the follow-up visit (Appendix 4).

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 29±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 19.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 19 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 29±2 days.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until the follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 29±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

This study includes a screening period (Day -28 to Day -3 [or Day -5 depending on the clinical site's requirement for COVID-19 testing]), a treatment period (Days -2 [or Day -4] to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2 or Day -4 depending on the clinical site's requirement for COVID-19 testing) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

7.1. General Assessments

7.1.1. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.1.2. Medical History

At the timepoint specified in Appendix 6, the investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

Continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. All ECG data will be collected using a Holter (or Mortara Surveyor) ECG continuous 12-lead digital recorder. The 12-lead Holter (or Mortara Surveyor) ECG equipment will be supplied and supported by ERT (eResearch Technology Inc., Philadelphia, PA). The continuous 12-lead digital ECG data will be stored onto SD memory cards.

The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT (eResearch Technology Inc., Philadelphia, PA). The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints and subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter (or Mortara Surveyor) recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically,

the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position).

7.2.1.2. Expert Precision QT Analysis

Expert precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc, or RR from beat-to-beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR values from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS interval of the ECG (QRS) intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed (ie, changes not present at baseline). For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline.

7.2.2. Safety 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria applies:

- QT interval corrected for HR using Fridericia's method (QTcF) is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.3. Cardiac Telemetry Monitoring

Subjects will be monitored via cardiac telemetry from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days; as described in Appendix 6). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary.

The start and stop date and time of the telemetry monitoring will be recorded in the eCRFs. Clinically significant abnormalities noted from telemetry monitoring will be confirmed by 12-lead ECG if necessary, then after confirming, the abnormities will be reported as AEs in the eCRF.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 × 4 mL for CBP-307 and moxifloxacin assays) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of CBP-307 and moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the follow-up visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of placebo administration to all subjects (Day -1) until study completion. If AEs that occur in the screening prior to placebo administration to all subjects (Day -1) are considered to be related to the study procedure, they should be also collected. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator’s (or designee’s) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

A serum qualitative pregnancy or urine test (females only) and follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test. All pregnancies should be reported as specified in Appendix 1.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. At the discretion of the investigator, clinically significant clinical laboratory assessments may be confirmed by repeat sampling. If the clinical significance is confirmed, subjects will be excluded from participation or, if already included, will be followed until normalization of the test result or for as long as the investigator considers necessary.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.4.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and tympanic temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Physical examinations include general appearance, head, eyes,

ears, nose, and throat, neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, skin, and others.

Height, weight, and body mass index will be assessed at screening.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 68 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 34 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 17 subjects.

Sample Size for Primary Analysis:

A sample size of 28 evaluable subjects per treatment group will provide more than 94.4% power to exclude that CBP-307 causes more than 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QT effect (ΔΔQTcF) at the observed geometric mean C_{max} of CBP-307 in the study. This power is estimated approximately using a 2-sample t-test. The calculation assumes a 1-sided 5% significance level, an underlying effect of CBP-307 of 3 msec and a standard deviation (SD) of the ΔQTcF of 8 msec for both CBP-307 and placebo treatment groups. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed-effects model. The concentration-QTc analysis method is supported by Darpo et al 2015[3] and Ferber et al, 2015,[4] and consistent with the experiences from 25 recent TQT studies.

Sample Size Considerations for Assay Sensitivity:
To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.64 required to guarantee a power of at least 95% in a paired t-test situation with a sample size of 28 evaluable subjects. In other words, based on this calculation, a power of at least 95% will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD from the by-timepoint analysis, does not exceed 6.9 msec (ie, 128% [= 0.82/0.64] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects.[5]

8.2. Analysis Populations

8.2.1. Cardiodynamic Population

The QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value. The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

The PK/QTc population will include all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for CBP-307, and for moxifloxacin.

The as-treated principle will be applied to all analysis populations mentioned below.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of investigational product and have evaluable PK data of any of the analytes (CBP-307 and moxifloxacin). A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of investigational product drug (therapeutic and supratherapeutic doses of CBP-307, moxifloxacin, or placebo).

8.3. Cardiodynamic ECG Analyses

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1 (defined as Period 1 Day 1), baseline will be Day 16 (defined as Period 1 Day -1), on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 (defined as Period 2 Day 1) on which subjects are administered placebo, and baseline will be obtained on Day -1 (defined as Period 2 Day -1).

- Group 2B: For moxifloxacin administered on Day 16 (defined as Period 2 Day 1), baseline will be Day 1 (defined as Period 2 Day -1), on which subjects are administered placebo. For the placebo-correction in this group, Day -1 (defined as

Period 1 Day 1) values will be used as placebo (no treatment) and baseline will be obtained on Day 15 (defined as Period 1 Day -1).

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6] Centered baseline QTcF (i.e., baseline QTcF for individual subject minus the population mean baseline QTcF for all subjects) will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term.

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-timepoint analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 6, and 15, and Days 1 and 16 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 6 and 15 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 6 and 15 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max} <10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 6 and 15; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 6 and 15; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 6 and 15, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-timepoint analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), period (as described in baseline definition for assay sensitivity), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint on Day 1, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

8.4. Pharmacokinetic Analyses

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, SD, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by group. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_Z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Other parameters may be added as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the Statistical Analysis Plan.

8.5. Safety Analysis

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

8.6. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication.

Examples of AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving clinically significant abnormal laboratory tests, ECG, etc.)
- Exacerbation of previous condition, including increased incidence and/or severity.

Note: Regarding decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. All AEs will be recorded in the medical records and eCRFs. The investigator (or designee) is to record in detail any AE that occurred to the subject, including: AE diagnosis whenever possible, or signs, symptoms, the start date and time of occurrence, the stop date and time of occurrence, seriousness (ie, whether it is an SAE), severity of AEs, causality assessment, actions taken on the investigational product, other actions (eg, medications/treatments given), and outcomes of AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: 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, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

All SAEs will be collected after subjects sign the informed consent form and throughout the entire study, ie, until the end-of-study as specified in the protocol (or at early termination).

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor (or designee).

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to:
+61-2-8879-2000 (AUS) or 1-888-887-8097 (US)

SAE Reporting email: SAEIntake@labcorp.com (preferred method)

Labcorp Safety SAE Reporting Fax Numbers: 61-2-6100-9788 or 1800-882-203 (toll free) in Australia and 1-888-887-8097 (toll free) in the US

The responsibilities of Labcorp Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the IRB/EC, Medicines and Healthcare Products Regulatory Agency, FDA, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

For SAEs, the active reporting period to sponsor or its designated representative begins from the time that the subject provides informed consent through to the last subject visit.

Nonserious AEs should be collected from the time the subject has taken the placebo dose on Day -1 through the last subject visit. If AEs that occur in the screening prior to the placebo administration to all subjects on Day -1 are considered to be related to the study procedure, they should be also collected.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, the sponsor should be notified within 24 hours of investigator awareness of the event. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting as specified above. In addition, an investigator

may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

If the female subject becomes pregnant during the clinical trial and has not yet been dosed with study treatment, she must be withdrawn from the study. If the female subject becomes pregnant during the clinical trial and has been dosed, she must discontinue treatment immediately but may remain on study for safety evaluations. If the partner of a male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should report to the sponsor or designee in a pregnancy report form within 24 hours after investigator awareness and report to the IRB/EC in time as per local requirement.

The investigator will follow up on pregnancy outcomes, until not less than 12 months after birth, unless otherwise justified, and will report the outcome to the sponsor and IRB/EC.

If any adverse pregnancy outcome (eg, the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformations), it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if indicated by dipstick)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen Syphilis	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol Tricyclic antidepressants Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b] **Other Tests** Low density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at check-in (on Day -4 or Day -2 depending on the clinical site's requirements for Coronavirus Disease 2019 testing) and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	41	328
Total:			390.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the follow-up visit. Primary (non-barrier) methods of contraception include:

- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation or bilateral salpingectomy
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- non-hormonal intrauterine device or Mirena® (other hormonal intrauterine devices will not be allowed) in place for at least 3 months prior to the first dose of the study drug
- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom without spermicide
- female condom without spermicide
- cervical cap without spermicide (as prescribed)
- diaphragm without spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2 or Day -4 depending on the clinical site's requirement for COVID-19 testing) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom without spermicide) in addition to a second method of acceptable contraception from check-in until 90 days after the follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- cervical cap without spermicide
- diaphragm without spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal,

postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol, local legal and regulatory requirements and with the following:

- General principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the institutional review board (IRB)/human research ethics committee (HREC) by the investigator and reviewed and approved by the IRB/HREC before the study is initiated.

Any protocol amendments will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB/HREC. All correspondence with HREC should be retained in the investigator file. A copy of /IRB/HREC approval should be forwarded to the sponsor.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/EC, and all other applicable local regulations.

Regulatory Authority

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following the discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive in accordance with 21 CFR 312.62(c) or for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed as follows:The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3 (or -5 if needed for COVID-19 testing)** [1]	**-2 (or -4 if needed for COVID-19 testing)** [1]	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													

Schedule of Assessments

Study Period	**Screening**	**In-house Treatment Period**												**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3 (or -5 if needed for COVID-19 testing)** [1]	**-2 (or -4 if needed for COVID-19 testing)** [1]	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X	X				
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COVID-19 = Coronavirus Disease 2019; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 to 4 days before start of dosing on Day 1 (on Day -4 or Day -2 depending on the clinical site's requirements for COVID-19 testing).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at check-in (Day -4 or Day -2) and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 hour postdose, ±15 minutes for ECGs and vital sign measurements at 2 hours postdose and ±5 minutes for PK sampling at 2 hours postdose, ±5 minutes for 3 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Summary of Amended Protocol Changes

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 3 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021
Protocol Amendment 2 Date: 03 August 2021
Protocol Amendment 3 Date: 26 October 2021
Protocol Version: 4.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Covance Study Number: 8463245
IND Number: 134585

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The primary changes in this amendment, along with the rationale for each change as appropriate, are:

1. Based on recommendations from the regulatory agency, the protocol was modified to add baseline QTc as a fixed effect in the concentration-QTc model and a period effect (i.e., Day effect) to the mixed model for moxifloxacin by-timepoint analysis so that the analysis will be appropriate for the crossover design of the moxifloxacin and placebo parts of the study.
2. To update the protocol to modify Inclusion Criterion 6a regarding electrocardiogram findings for heart rate. The allowable range for heart rate was changed from 60 to 100 bpm to 55 to 100 bpm.
3. To modify the number of sites enrolling subjects in the study to include an additional site in the United States. As a result, the regulatory and contact information was revised to include the Institutional Review Board (IRB), Investigator, and clinical laboratory in the United States. Revised serious adverse event reporting as needed. Removed mention of the specific pharmacy for the site in Australia as there will be a pharmacy at each of the sites.
4. Revised the bioanalytical laboratory contracted to perform the analysis for the study.
5. Updated title to reflect the modification from a single site to multiple sites.
6. To modify the pharmacokinetic endpoints to remove the accumulation ratios.

Minor changes:

1. The protocol version and date were updated throughout the protocol.
2. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below:

Synopsis and Title Page, Title

Previously read:

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Now reads:

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Synopsis and Section 3.1, Study Design, first paragraph

Previously read:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Now reads:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, multi-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Study Identification Section (pages 5 and 6), Study Sites, Principal Investigators, and Clinical Laboratories (Title page now includes shared content from this page)

Previously read:

Study Site	CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia
Principal Investigator	Nicholas Farinola, MBBS CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia Tel: (08) 7088 7900 Email: nicholas.farinola@sa.gov.au
Clinical Laboratory	Australian Clinical Laboratories 1 Butler Boulevard Adelaide Airport Adelaide, South Australia 5950 Australia
Bioanalytical Laboratory	Peter Tapley Director, TetraQ The University of Queensland Level 7, Block 6, RBWH Herston, Queensland 4029 Australia

Now reads:

Study Sites	CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia CPMI, LLC 550 West 84th Street Hialeah, Florida 33014 United States
Principal Investigators	Nicholas Farinola, MBBS CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia Tel: (08) 7088 7900 Email: nicholas.farinola@sa.gov.au Juan Carlos Rondon, MD, JD, CPI, FCLM CPMI, LLC 550 West 84th Street Hialeah, Florida 33014 United States Tel: 1-305-817-2900 Email: jrondon@ergclinical.com
Clinical Laboratories	Australian Clinical Laboratories 1 Butler Boulevard Adelaide Airport Adelaide, South Australia 5950 Australia Ecco Lab Group 8370 West Flagler Street, Suite 216 Miami, Florida 33144 United States Tel: 1-305-220-3805
Bioanalytical Laboratory	Margaret Mathews Director Agilex Biolabs 28 Dalgleish Street Thebarton, South Australia 5031 Australia

Section 4.1, Inclusion Criterion 6a

Previously read:

Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive)

Now reads:

Normal sinus rhythm (HR between 55 bpm and 100 bpm inclusive)

Section 4.5 and Appendices 1 and 5, added institutional review board (IRB; where applicable).

Previously read:

ethics committee (EC) or human research ethics committee (HREC)

Now reads:

institutional review board (IRB)/ethics committee (EC) or institutional review board (IRB)/human research ethics committee (HREC)

Section 5.6, Drug Accountability, paragraph 3

Previously read:

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy, per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy (RAH Pharmacy), the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

Now reads:

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy, per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

Section 8.3, Cardiodynamic ECG Analyses, Baseline for Cardiodynamic ECG Assessments (where applicable)

Previously read:

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 16, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 16, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 15.

Now reads:

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1 (defined as Period 1 Day 1), baseline will be Day 16 (defined as Period 1 Day -1), on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 (defined as Period 2 Day 1) on which subjects are administered placebo, and baseline will be obtained on Day -1 (defined as Period 2 Day -1).

- Group 2B: For moxifloxacin administered on Day 16 (defined as Period 2 Day 1), baseline will be Day 1 (defined as Period 2 Day -1), on which subjects are administered placebo. For the placebo-correction in this group, Day -1 (defined as Period 1 Day 1) values will be used as placebo (no treatment) and baseline will be obtained on Day 15 (defined as Period 1 Day -1).

Section 8.3, Cardiodynamic ECG Analyses, Concentration-QTc Analysis (Primary Analysis), first paragraph.

Previously read:

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6]

Now reads:

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6,

and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6] Centered baseline QTcF (i.e., baseline QTcF for individual subject minus the population mean baseline QTcF for all subjects) will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term.

Section 8.3, Cardiodynamic ECG Analyses, By-Timepoint Analysis, paragraphs 1 and 2

Previously read:

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP 307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

Now reads:

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), period (as described in baseline definition for assay sensitivity), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint on Day 1, respectively.

Section 8.4 Pharmacokinetic Analyses, accumulation ratio

Previously read:

- Accumulation ratio (R_{ac}) for C_{max} ($R_{ac[Cmax]}$) and $R_{ac(AUC0-24)}$, calculated as Day 15 C_{max}/Day 7 C_{max} and Day 15 AUC_{0-24}/Day 7 AUC_{0-24}, respectively.

Now reads:

(removed)

Appendix 1, Adverse Event Reporting, Serious Adverse Event Reporting, Contact Information (where applicable)

Previously read:

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp APAC Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to: +61-2-8879-2000

SAE Reporting email: SAEIntake@labcorp.com (preferred method)

Labcorp Safety SAE Reporting Fax Number: 61-2-6100-9788 or 1800-882-203 (toll free)

The responsibilities of Labcorp APAC Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp APAC Drug Safety who will delete any information from the SAE report forms that may identify the subject.

- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the EC, Medicines and Healthcare Products Regulatory Agency, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

Now reads:

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to:
+61-2-8879-2000 (AUS) or 1-888-887-8097 (US)

SAE Reporting email: SAEIntake@labcorp.com (preferred method)

Labcorp Safety SAE Reporting Fax Numbers: 61-2-6100-9788 or 1800-882-203 (toll free) in Australia and 1-888-887-8097 (toll free) in the US

The responsibilities of Labcorp Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the IRB/EC, Medicines and Healthcare Products Regulatory Agency, FDA, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

Appendix 5, Regulatory, Ethical, and Study Oversight Considerations, Data Quality Assurance, last bullet point

Previously read:

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Now reads:

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive in accordance with 21 CFR 312.62(c) or for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Protocol

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 3 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021
Protocol Amendment 2 Date: 03 August 2021
Protocol Amendment 3 Date: 26 October 2021
Protocol Version: 4.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Labcorp Study Number: 8463245
IND Number: 134585

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SPONSOR APPROVAL

I have read the protocol and approve it:

DocuSigned by:
签名者名称： Ping Li
签名原因： 我批准此文档
签名时间： 26 10月 2021 | 5:41:42 下午 PDT
4C556BD566CD4EA4B8BFEB77ED35D596

Ping Li, MD Date
VP, Clinical Development Asia

INVESTIGATOR AGREEMENT

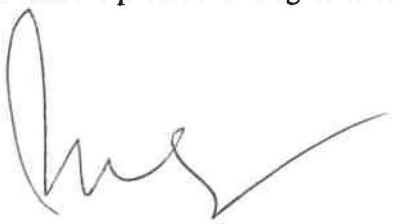
I have read the protocol and agree to conduct the study as described herein.

DocuSigned by:
Signer Name: Nicholas Farinola
Signing Reason: I approve this document
Signing Time: 26 Oct 2021 | 10:09:12 PM PDT
41E77C67C07F4FF8811CE7A5D4536EB8

Nicholas Farinola, MBBS Date
Principal Investigator
CMAX

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.



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STUDY IDENTIFICATION

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SYNOPSIS

Study Title

A Phase I, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the pharmacokinetics (PK) of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on heart rate (HR), PR and QRS intervals, and T-wave morphology.

Study Design

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, multi-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on

Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a

supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Number of Subjects

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 titrated to 0.1 mg on Day 2; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)
- Moxifloxacin (400 mg; oral tablet).

Duration of Subject Participation in the Study

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 21 days for the in-house treatment period (Days -2 to 19), and 10 ±2 days for follow-up (Day 29±2 days), in total approximately 59 days.

Endpoints

Electrocardiogram (Cardiodynamic):

The primary cardiodynamic endpoint is the change-from-baseline QTcF (ΔQTcF).

The secondary cardiodynamic endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);
- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CBP-307. The PK parameters of CBP-307 will be calculated using a model independent approach. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}), and time of the maximum observed concentration (t_{max}). Other noncompartmental parameters may be reported.

Safety:

Adverse events, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12lead ECGs, and vital signs measurements.

Statistical Methods

Cardiodynamic evaluation:

The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of CBP-307 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma levels. Placebo-corrected ΔHR, ΔPR, ΔQRS, and ΔQTcF (ΔΔHR, ΔΔPR, ΔΔQRS, and ΔΔQTcF) will also be evaluated at each postdosing timepoint ('by-timepoint'

analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.

Pharmacokinetics:

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by cohort. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

Pharmacokinetic/electrocardiography analyses:

The relationship between CBP-307 plasma concentrations and the change from ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12lead ECGs, vital signs, and physical examination findings will be listed.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CRO	contract research organization
CYP	cytochrome P450
Δ	change-from-baseline
ΔΔ	placebo-corrected or placebo-adjusted change-from-baseline
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HR	heart rate
HREC	human resource ethics committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
IRB	institutional review board
LOESS	locally estimated scatterplot smoothing
LS	least squares
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
QD	once daily
QTc	heart-corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method

SAE	serious adverse event
SD	standard deviation
SE	standard error
S1P1	sphingosine-1-phosphate receptor 1
TEAE	treatment-emergent adverse event(s)
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
TQT	thorough QT
V_z/F	apparent volume of distribution
WBC	white blood cell
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the investigator's brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Disease Background

Autoimmune diseases are serious disorders that afflict a large portion of the world population; most have no cures. Significant advances have been made in the development of novel and disease-modifying therapies, but many of these new treatments have significant side effects. Treatments are needed that provide better risk-to-benefit profiles than the existing therapeutic choices.

T cells are important immune cells that mediate the development of autoimmune disorders. Migration of T cells from lymphoid tissues to the sites of inflammation is central to the functions of T cells, and this process is dependent on sphingosine-1-phosphate (S1P) receptor 1 (S1P1) which is known to ameliorate a variety of autoimmune diseases in animals and humans. Down modulation of this receptor, using S1P1 agonists, prevents T cell egress and results in a reduced number of circulating lymphocytes, particularly the CD4+- and CD8+-naïve and central-memory T cell subsets.

1.2. Overview of CBP-307

CBP-307 is an S1P1 agonist that is being developed as a treatment for autoimmune diseases by Suzhou Connect Biopharmaceuticals, Ltd. CBP-307 (1-(2-fluoro-4-(5-(4-isobutylphenyl)-1,2,4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid hemihydrate) is a potent, selective, small-molecule agonist of S1P1 and S1P5 receptors. Cell-based assays have confirmed CBP-307 induces internalization of S1P1 from the cell surface. This is consistent with the known mechanism of action of other S1P1 agonists, in that they down-modulate S1P1 and inhibit lymphocyte egress from lymphoid tissues.

1.2.1. Summary of Clinical Experience

The Phase 1 development of CBP-307 comprised 2 completed studies in healthy subjects:

- A single and multiple ascending dose study to evaluate the safety and tolerability of CBP-307 including pharmacokinetic (PK), pharmacodynamic (PD), and food-effect assessments (Study CBP-307AU001)
- A single-dose and multiple-dose, and fixed-dose titration study to evaluate the safety and tolerability of CBP-307 including PK and PD (Study CBP-307CN001)

Currently, CBP-307 is being evaluated in 2 Phase 2 studies:

- Ongoing multicenter study in subjects with moderate to severe ulcerative colitis (Study CBP-307CN002) to compare the clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing

achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

- Ongoing study in subjects with moderate to severe Crohn's disease compares clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

1.2.1.1. Safety

Study CBP-307AU001

A total of 44 healthy subjects were enrolled in the study. There were 28 subjects evaluated using the single-dose regimen (0.1, 0.25, 0.5, and 2.5 mg CBP-307) of which 21 subjects received CBP-307 and 7 subjects received placebo. Another 16 healthy subjects were evaluated using the multiple-dose regimen (0.15 and 0.25 mg CBP-307 given once daily [QD] for 28 consecutive days) of which 12 subjects received CBP-307 and 4 subjects received placebo.

Overall, no unexpected safety signals were identified and no deaths occurred in this study. For the single-dose regiment, no subjects were discontinued due to a treatment-emergent AE (TEAE). In the multiple-dose regimen, there were 2 subjects who were discontinued from the study (due to increased alanine transaminase and second degree AV block [not considered to be clinically significant, as judged by the investigator]). All TEAEs resolved by the end of the study.

In the single-dose regimen groups, TEAEs were reported in 12 of 21 subjects (57.1%) treated with CBP-307 and in 3 of 7 subjects (42.8%) treated with placebo. Most (91.7%) of the TEAEs in these subjects were mild in severity. The most common TEAEs in the CBP-307-treated groups were headache (28.6%); dizziness (19.0%); and bradycardia (9.5%). Bradycardia was reported only in 2 subjects receiving the highest (2.5 mg) CBP-307 dose. One subject had a serious adverse event (SAE) of bradycardia (associated with transient asystole) following a single dose of 2.5 mg CBP-307.

In the multiple-dose regimen groups, CBP-307 at doses of 0.15 and 0.25 mg QD was generally well tolerated over the 28 days of dosing. Treatment-emergent AEs were reported in 11 of 12 subjects (91.7%) in the CBP-307 groups and 2 of 4 subjects (50.0%) in the placebo groups. Most (83.3%) TEAEs were mild in severity. The most common TEAEs in the 2 CBP-307 groups were headache (50.0%), and fatigue, nausea, and musculoskeletal pain (16.7% each). The incidences of these TEAEs were similar in both CBP-307-treated groups. No SAEs were reported for subjects in the multiple-dose regimen.

Study CBP-307CN001

A total of 30 eligible subjects completed 3 CBP-307 dose groups in ascending order of dose after randomization (in a ratio of 1:1:1): Group A (0.1 mg), Group B (0.2 mg), and Group C (0.3 mg). Each dose group consisted of 10 subjects, including 8 subjects receiving the investigational drug and 2 subjects receiving placebo by random assignment. The administration started from the dose of 0.1 mg. The subjects in this group received a single

dose of CBP-307 or placebo and were followed up for safety and tolerance within the next 7 days. Then the subjects received 0.1 mg CBP-307 or placebo QD for 14 consecutive days and were followed up for safety and tolerance within the next 7 days. Dose escalation did not occur until the review of the single-dose regimen safety data from the 6 subjects in the previous dose cohort, and the safety data did not meet the termination criteria. The subjects in the dose of 0.3 mg received fixed-dose titration regimen, ie, 0.05 mg CBP-307 or placebo QD for 3 consecutive days; 0.1 mg CBP-307 or placebo QD for 2 consecutive days; 0.2 mg CBP-307 or placebo QD for 2 consecutive days; finally, 0.3 mg CBP-307 or placebo QD for 14 consecutive days, and the subjects were followed up for safety and tolerance within the next 7 days.

Overall, no unexpected safety signals were identified, and there were no deaths, SAEs, or AEs leading to the subject's early withdrawal from the study after administration of CBP-307. In the safety set, a total of 29 subjects (8 in Group A, 100%; 8 in Group B, 100%; 8 in Group C, 100% and 5 in placebo group, 83.3%) experienced TEAEs.

During the single-dose period, a total of 14 subjects (5 of 8 in Group A, 62.5%; 6 of 8 in Group B, 75%, and 3 of 4 in placebo group, 75%) developed AEs. The incidence of TEAEs in Group A was generally similar to the placebo group. Among TEAEs in Group B, the incidence of AEs related to abnormalities in investigations was higher than that in placebo group, including lymphocyte count decreased (12.5%), white blood cell (WBC) count decreased (12.5%), neutrophil count decreased (12.5%), alanine aminotransferase increased (25%), and gamma-glutamyltransferase increased (12.5%), and aspartate aminotransferase increased (12.5%). Additionally, 1 subject experienced heart rate (HR) decreased (12.5%).

During dose-titration period, 2 subjects (2 of 8 in Group C, 25%) experienced TEAEs. The TEAEs reported in Group C during the titration period included cough (12.5%) and increased upper airway secretion (12.5%). There were no TEAEs in the placebo group during this period.

During repeated-dose period, a total of 28 subjects (8 of 8 in Group A, 100%; 8 of 8 in Group B, 100%; 8 of 8 in Group C, 100%; and 4 of 6 in placebo group, 66.7%) experienced AEs. The most frequent TEAE in Group A was upper respiratory tract infection (37.5%) compared with placebo group; the most frequent TEAEs in Group B and Group C included decreased lymphocyte count (Group B, 87.5%; Group C, 100.0%), WBC count (Group B, 87.5%; Group C, 62.5%), and neutrophil count (Group B, 50%; Group C, 12.5%). The TEAEs noted in Group B during the repeated-dose period also included increased alanine aminotransferase (25%), gamma-glutamyltransferase (37.5%), and aspartate aminotransferase (12.5%), upper respiratory tract infection (12.5%), influenza (12.5%), chest pain (12.5%), lethargy (25%), and neck pain (12.5%); TEAEs in Group C during the repeated-dose period also included increased alanine aminotransferase (25%), decreased HR (12.5%), and mouth ulcer (12.5%); the TEAEs in placebo group included increased transaminase (16.7%), prolonged activated partial thromboplastin time (1/6, 16.7%), decreased hemoglobin (16.7%), upper respiratory tract infection (16.7%), diarrhea (16.7%), dizziness (16.7%), and palpitations (16.7%).

Study CBP-307CN002

This study is ongoing and there are no safety data available.

Study CBP-307CN003

This study is ongoing and there are no safety data available.

1.2.1.2. Pharmacokinetics

CBP-307 given orally as a single dose was readily absorbed; drug concentrations peaked at approximately 6 hours after administration, with an elimination apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours (range of 23 to 29 hours). The time to maximum observed concentration (C_{max}) in the blood was delayed from 6 hours to approximately 10 hours when CBP-307 was given with a high-fat diet. Food consumption also increased exposure (Table 1).

For the single-dose administration, CBP-307 exposure (based on C_{max} and area under the concentration-time curve [AUCs]) increased with increasing dose following a single-dose administration (Table 1).

Table 1: Pharmacokinetics Parameters in the Single-Dose CBP-307 Regimen (Study CBP-307AU001)

Single-Dose Regimen PK Parameters	Mean CBP-307 Single Dose ± SEM (n)				
	0.1 mg	**0.25 mg**	**0.5 mg (fasted)**	**0.5 mg (fed)[a]**	**2.5 mg**
AUC_{last} (ng*h/mL)	13.4 ± 3.54 (n = 6)	45.1 ± 5.25 (n = 6)	160 ± 22.8 (n = 6)	290 ± 28.1 (n = 6)	550 ± 96.3 (n = 3)
AUC_{inf} (ng*h/mL)	ND	63.7 ± 2.14 (n = 3)	214 ± 58.3 (n = 3)	355 ± 44.3 (n = 5)	710 ± 164 (n = 2)
C_{max} (ng/mL)	0.537 ± 0.0931 (n = 6)	1.53 ± 0.0935 (n = 6)	4.84 ± 0.706 (n = 6)	8.58 ± 1.11 (n = 6)	19.0 ± 3.55 (n = 3)
t_{max} (hours)	7.33 ± 1.33 (n = 6)	5.33 ± 0.99 (n = 6)	5.00 ± 0.86 (n = 6)	10.67 ± 2.72 (n = 6)	6.00 ± 2.00 (n = 3)
$t_{1/2}$ (hours)	ND	23.3 ± 1.70 (n = 3)	28.8 ± 1.28 (n = 3)	26.0 ± 1.17 (n = 5)	22.8 ± 3.96 (n = 2)

Abbreviations: AUC_{inf} = area under the curve at infinity; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; h = hour(s); mg = milligram(s); ND = not determinable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SEM = standard error of the mean; $T_{1/2}$ = elimination half-life; t_{max} = time to maximum concentration.
[a] Study Part 1b: Cohort 3 from Part 1a returned to receive a single oral dose of CBP-307 at 0.5 mg under fed conditions.
Source: Final report for Study CBP-307AU001.

For the repeated-dose administration of CBP-307, the C_{max} and AUCs increased with the higher administered dose (Table 2). At the steady-state timepoint on Day 28, the median CBP-307 t_{max} was 4 to 6 hours. The average $t_{1/2}$ was similar, ranging 44 to 49 hours, and there were no dose-dependent changes in $t_{1/2}$ within the dose range. The $t_{1/2}$ was slightly prolonged after repeated-dose administration when compared with that after a single-dose administration. Moderate accumulation of CBP-307 (approximately 3 times the levels

following a single dose) was noted in plasma after QD administration for 14 consecutive days.

Table 2: Pharmacokinetics Parameters in the Multiple-Dose CBP-307 Regimen (Study CBP-307AU001)

Multiple-Dose Regimen PK Parameters	Multiple-Dose Cohort 1 CBP-307 Dosing, mg (± SD) (n)		Multiple-Dose Cohort 2 CBP-307 Dosing, mg (± SD) (n)	
	Day 1 0.1	Day 28 0.25	Day 1 0.15	Day 28 0.15
AUC_{0-24} (ng*h/mL)	24.5 ± 3.26 (n = 5)	125 ± 12.4 (n = 4)	26.3 ± 7.45 (n = 5)	79.7 ± 27.3 (n = 6)
AUC_{last} (ng*h/mL)	NA	203 ± 21.9 (n = 4)	NA	131 ± 44.7 (n = 6)
C_{max} (ng/mL)	1.45 ± 0.214 (n = 5)	6.30 ± 0.588 (n = 4)	1.32 ± 0.422 (n = 6)	4.23 ± 1.45 (n = 6)
t_{max} (hours)	6.80 ± 1.50 (n = 5)	6.50 ± 1.50 (n = 4)	5.00 ± 0.68 (n = 6)	4.33 ± 0.33 (n = 6)

Abbreviations: AUC_{0-24} = area under the curve from time 0 to 24 hours; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; mg = milligram(s); NA = not applicable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SD = standard deviation; t_{max} = time to maximum concentration.
Source: Final report for Study CBP-307AU001.

1.3. Overview of Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of International Council for/Conference on Harmonisation (ICH) E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[2]

1.4. Study Rationale

Regulatory guidance (ICH E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase 1, 2, and 3 trials may be conducted they usually have an insufficient sample size, infrequent sampling of ECG data, or the use of inadequate controls to overcome the high rate of spontaneous change in QTc duration. This has resulted in regulatory guidance recommending a dedicated or thorough trial to define the ECG effects of new drugs.

This study will be done in healthy subjects to eliminate variables (concomitant drugs, diseases, etc.) known to have an effect on ECG parameters. A supratherapeutic dose of CBP-307 is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (eg, concomitant use of cytochrome P450

[CYP]3A4 inhibitor, concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to allow for PK to QTc modeling to assess the effect of drug concentration on cardiac repolarization.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with CBP-307 may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the PK of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on HR, PR and QRS intervals, and T-wave morphology.

2.2. Endpoints

2.2.1. Electrocardiogram Endpoints

2.2.1.1. Primary

The primary endpoint is the change-from-baseline QTcF (ΔQTcF).

2.2.1.2. Secondary

The secondary endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);

- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

2.2.2. Pharmacokinetic Endpoints

Pharmacokinetic parameters of CBP-307 will be determined if data allows:

- area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf})
- area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})

Other PK parameters may also be reported.

2.2.3. Safety Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, multi-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether

volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

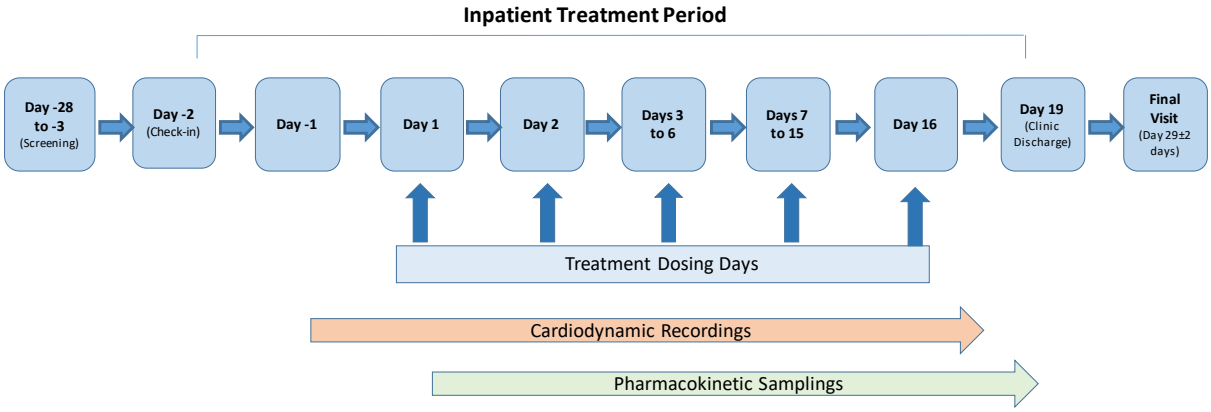
The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Day 2, Days 3 to 6, Days 7 to 15, and Day 16. Dosing details are provided in Table 3. Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. An end-of-study visit will occur on Day 29±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for CBP-307 to cause QT prolongation. As CBP-307 exposure affects heart rate, the primary endpoint for this study will be the QTcF.

The study will be randomized and double-blind because randomization eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions, thus eliminating the possibility that the observed effects of the intervention are because of differential use of other treatments.

The sample size for this study is based on a formal statistical power calculation.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Both male and female subjects will be included to eliminate similar known ECG variability effects.

Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Pharmacokinetic assessments of CBP-307 concentrations in plasma will be evaluated during the study. The timepoints for the PK sample collections are based on previous studies and are considered adequate to allow for the characterization of the drug's PK after oral dosing. Furthermore, the chosen PK sample collection for CBP-307 is anticipated to be sufficient to allow reasonable estimation of $t_{1/2}$ during the terminal elimination phase.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.05 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2 and a dose of 0.2 mg on Days 3 to 6. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index between 18.0 and 30.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and confirmed at check-in as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4. Negative pregnancy test for females of childbearing potential at screening (blood test) and check-in (urine test).
5. Supine diastolic blood pressure between 60 and 90 mmHg and systolic blood pressure between 90 and 140 mmHg (inclusive) at screening on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest.
6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 55 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.
7. Has serum potassium, calcium, and magnesium levels within the normal reference range at screening, as judged by the investigator.
8. Able to swallow multiple tablets (based on subject's verbal confirmation).
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Subject is mentally or legally incapacitated or has had significant history of recent mental health issues requiring medication and/or hospitalization at the time of the screening visit or expected during the conduct of the study.

2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee). *Note: Childhood asthma that is considered recovered or seasonal allergies that are not currently active or requiring treatment are allowed.*
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
4. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
5. History of significant multiple and/or severe allergies (eg, latex allergy, band-aids, adhesive dressing, or medical tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.
6. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs within 6 months prior to the first dose of study drug (uncomplicated appendectomy and hernia repair will be allowed).
7. History or presence of:
    a. Hypokalemia, in the opinion of the investigator (or designee);
    b. Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
    c. Sick sinus syndrome, second, or third degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities;
    d. Repeated or frequent syncope or vasovagal episodes;
    e. Hypertension, angina, bradycardia, or severe peripheral arterial circulatory disorders.
8. Clinically significant abnormalities (as judged by the investigator in laboratory tests results [out-of-range results confirmed on repeat]), including but not limited to the following parameters:
    a. alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin greater than 1.5 × upper limit of normal;
    b. hemoglobin <10 g/dL, WBC <3.0 $\times 10^9$/L, neutrophils <1.5 $\times 10^9$/L, lymphocytes <0.8 $\times 10^9$/L and platelets <100 $\times 10^9$/L or >1200 $\times 10^9$/L;
9. History or evidence of alcoholism or drug/chemical abuse within 12 months prior to check-in.
10. Alcohol consumption of >10 units per week for males and females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
11. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.

12. Positive hepatitis panel, positive syphilis test, and/or positive human immunodeficiency virus test (Appendix 2).
13. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 28 days prior to the first dose of study treatment on Day 1. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
14. Participation in a previous clinical study where subjects received CBP-307.
15. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 28 days prior to first dose of study treatment on Day 1.
16. Use or intend to use any prescription medications/products within 14 days prior to first dose of study drug (Day 1) and throughout the study, unless deemed acceptable by the investigator (or designee). *Note: For females only, the use hormonal contraception, hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives within 14 days prior to Day 1 is not acceptable, except for Mirena®.*
17. Use or intend to use any drugs known to be significant inhibitors or inducers of CYP enzymes and/or P-gp, including St. John's Wort, for days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the investigator or designee to confirm the lack of PK/PD interaction with the study drug.
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intend to use any nonprescription medications/products including antacids, vitamins (especially those containing magnesium, aluminum, iron, or zinc), minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
21. Has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for whatever reason), in the opinion of the investigator, within the 28 days prior to the first dose of study treatment, and throughout the study.
22. Consumption of caffeine/xanthine-containing foods or beverages within 48 hours prior to check-in until discharge.
23. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
24. Receipt of blood products within 2 months prior to check-in.
25. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
26. Poor peripheral venous access.

27. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Eligible subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). The screening number will be used on all safety samples throughout the study. Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw their informed consent from the study at any time or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, or the inability of the subject to comply with the protocol-required visits or procedures. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- investigator decides to terminate the study due to safety concerns such as AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development
- sponsor requests for termination (eg, due to financial or management reasons, etc.) under the premise to fully protect the safety and rights of subjects
- health authority or institutional review board (IRB)/ethics committee (EC) orders the termination of the trial for any reason.

Definition of end-of-treatment and end-of-study

- end-of-treatment is completion of safety follow-up or withdrawal from the study. End-of-study is the last visit by the last subject.

5. STUDY TREATMENTS

Study treatments are defined as any investigational product (IP), non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as IMP and non-IMP, respectively.

5.1. Investigational Products

The details regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 will be provided in a separate document. Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Table 3: Study Treatments

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1		1 capsule		1 tablet
	Group 2A		1 capsule		1 tablet
	Group 2B		1 capsule	1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

All supplies of the IMP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study treatments will be stored at the study site in a location that is locked with restricted access.

5.2. Study Treatment Administration

Each dose of study treatment (CBP-307, placebo, or moxifloxacin) will be administered orally following an overnight fast of at least 10 hours, with approximately 240 mL of room temperature water. Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Subjects will be dosed in numerical order while sitting or standing but not be permitted to lie supine for 2 hours after treatment administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a double-blind randomized study. Subjects will be randomized to one of the treatment sequences before administration of the first dose of study treatment. A randomization list will be generated by a statistician using a computer-generated pseudo-random permutation procedure. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the study site. Randomization details will be included in the randomization specification.

5.4. Blinding

This is a double-blinded study. The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to CBP-307 or moxifloxacin.
- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.
- Interim bioanalytical data will be provided to Labcorp Early Clinical Biometrics in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing coded details of the treatment. These individually sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until the completion of the study.

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy, per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from the use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the investigator (or designee) and/or sponsor have given their prior consent. Medications taken within 28 days before study treatment administration will be documented as a prior treatment. Treatments taken after study treatment administration will be documented as concomitant treatments.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for the treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Females will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives (with the exception of Mirena®) during the study until the follow-up visit (Appendix 4).

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 29±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 19.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 19 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 29±2 days.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until the follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 29±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

This study includes a screening period (Day -28 to Day -3), a treatment period (Days -2 to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

7.1. General Assessments

7.1.1. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.1.2. Medical History

At the timepoint specified in Appendix 6, the investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

Continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. All ECG data will be collected using a Holter (or Mortara Surveyor) ECG continuous 12-lead digital recorder. The 12-lead Holter (or Mortara Surveyor) ECG equipment will be supplied and supported by ERT (eResearch Technology Inc., Philadelphia, PA). The continuous 12-lead digital ECG data will be stored onto SD memory cards.

The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT (eResearch Technology Inc., Philadelphia, PA). The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints and subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter (or Mortara Surveyor) recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically,

the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position).

7.2.1.2. Expert Precision QT Analysis

Expert precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc, or RR from beat-to-beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR values from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS interval of the ECG (QRS) intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed (ie, changes not present at baseline). For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline.

7.2.2. Safety 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria applies:

- QT interval corrected for HR using Fridericia's method (QTcF) is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.3. Cardiac Telemetry Monitoring

Subjects will be monitored via cardiac telemetry from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days; as described in Appendix 6). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary.

The start and stop date and time of the telemetry monitoring will be recorded in the eCRFs. Clinically significant abnormalities noted from telemetry monitoring will be confirmed by 12-lead ECG if necessary, then after confirming, the abnormities will be reported as AEs in the eCRF.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 × 4 mL for CBP-307 and moxifloxacin assays) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of CBP-307 and moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the follow-up visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of placebo administration to all subjects (Day -1) until study completion. If AEs that occur in the screening prior to placebo administration to all subjects (Day -1) are considered to be related to the study procedure, they should be also collected. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator’s (or designee’s) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

A serum qualitative pregnancy or urine test (females only) and follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test. All pregnancies should be reported as specified in Appendix 1.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. At the discretion of the investigator, clinically significant clinical laboratory assessments may be confirmed by repeat sampling. If the clinical significance is confirmed, subjects will be excluded from participation or, if already included, will be followed until normalization of the test result or for as long as the investigator considers necessary.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.4.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and tympanic temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Physical examinations include general appearance, head, eyes,

ears, nose, and throat, neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, skin, and others.

Height, weight, and body mass index will be assessed at screening.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Sample Size for Primary Analysis:

A sample size of 28 evaluable subjects per treatment group will provide more than 94.4% power to exclude that CBP-307 causes more than 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QT effect (ΔΔQTcF) at the observed geometric mean C_{max} of CBP-307 in the study. This power is estimated approximately using a 2-sample t-test. The calculation assumes a 1-sided 5% significance level, an underlying effect of CBP-307 of 3 msec and a standard deviation (SD) of the ΔQTcF of 8 msec for both CBP-307 and placebo treatment groups. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed-effects model. The concentration-QTc analysis method is supported by Darpo et al 2015[3] and Ferber et al, 2015,[4] and consistent with the experiences from 25 recent TQT studies.

Sample Size Considerations for Assay Sensitivity:
To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.64 required to guarantee a power of at least 95% in a paired t-test situation with a sample size of 28 evaluable subjects. In other words, based on this calculation, a power of at least 95% will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD from the by-timepoint analysis, does not exceed 6.9 msec (ie, 128% [= 0.82/0.64] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects.[5]

8.2. Analysis Populations

8.2.1. Cardiodynamic Population

The QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value. The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

The PK/QTc population will include all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for CBP-307, and for moxifloxacin.

The as-treated principle will be applied to all analysis populations mentioned below.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of investigational product and have evaluable PK data of any of the analytes (CBP-307 and moxifloxacin). A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of investigational product drug (therapeutic and supratherapeutic doses of CBP-307, moxifloxacin, or placebo).

8.3. Cardiodynamic ECG Analyses

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1 (defined as Period 1 Day 1), baseline will be Day 16 (defined as Period 1 Day -1), on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 (defined as Period 2 Day 1) on which subjects are administered placebo, and baseline will be obtained on Day -1 (defined as Period 2 Day -1).

- Group 2B: For moxifloxacin administered on Day 16 (defined as Period 2 Day 1), baseline will be Day 1 (defined as Period 2 Day -1), on which subjects are administered placebo. For the placebo-correction in this group, Day -1 (defined as

Period 1 Day 1) values will be used as placebo (no treatment) and baseline will be obtained on Day 15 (defined as Period 1 Day -1).

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6] Centered baseline QTcF (i.e., baseline QTcF for individual subject minus the population mean baseline QTcF for all subjects) will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term.

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-timepoint analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 6, and 15, and Days 1 and 16 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 6 and 15 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 6 and 15 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max} <10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 6 and 15; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 6 and 15; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 6 and 15, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-timepoint analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), period (as described in baseline definition for assay sensitivity), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. Baseline QTcF will be included in this model as an additional covariate. If necessary, a sensitivity analysis will be performed using the model without this term. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint on Day 1, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

8.4. Pharmacokinetic Analyses

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, SD, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by group. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_Z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Other parameters may be added as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the Statistical Analysis Plan.

8.5. Safety Analysis

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

8.6. Interim Analysis

No interim analyses are planned for this study.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication.

Examples of AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving clinically significant abnormal laboratory tests, ECG, etc.)
- Exacerbation of previous condition, including increased incidence and/or severity.

Note: Regarding decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. All AEs will be recorded in the medical records and eCRFs. The investigator (or designee) is to record in detail any AE that occurred to the subject, including: AE diagnosis whenever possible, or signs, symptoms, the start date and time of occurrence, the stop date and time of occurrence, seriousness (ie, whether it is an SAE), severity of AEs, causality assessment, actions taken on the investigational product, other actions (eg, medications/treatments given), and outcomes of AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: 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, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

All SAEs will be collected after subjects sign the informed consent form and throughout the entire study, ie, until the end-of-study as specified in the protocol (or at early termination).

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor (or designee).

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to:
+61-2-8879-2000 (AUS) or 1-888-887-8097 (US)

SAE Reporting email: SAEIntake@labcorp.com (preferred method)

Labcorp Safety SAE Reporting Fax Numbers: 61-2-6100-9788 or 1800-882-203 (toll free) in Australia and 1-888-887-8097 (toll free) in the US

The responsibilities of Labcorp Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the IRB/EC, Medicines and Healthcare Products Regulatory Agency, FDA, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

For SAEs, the active reporting period to sponsor or its designated representative begins from the time that the subject provides informed consent through to the last subject visit.

Nonserious AEs should be collected from the time the subject has taken the placebo dose on Day -1 through the last subject visit. If AEs that occur in the screening prior to the placebo administration to all subjects on Day -1 are considered to be related to the study procedure, they should be also collected.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, the sponsor should be notified within 24 hours of investigator awareness of the event. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting as specified above. In addition, an investigator

may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

If the female subject becomes pregnant during the clinical trial and has not yet been dosed with study treatment, she must be withdrawn from the study. If the female subject becomes pregnant during the clinical trial and has been dosed, she must discontinue treatment immediately but may remain on study for safety evaluations. If the partner of a male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should report to the sponsor or designee in a pregnancy report form within 24 hours after investigator awareness and report to the IRB/EC in time as per local requirement.

The investigator will follow up on pregnancy outcomes, until not less than 12 months after birth, unless otherwise justified, and will report the outcome to the sponsor and IRB/EC.

If any adverse pregnancy outcome (eg, the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformations), it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if indicated by dipstick)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen Syphilis	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol Tricyclic antidepressants Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b] **Other Tests** Low density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	41	328
Total:			390.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the follow-up visit. Primary (non-barrier) methods of contraception include:

- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation or bilateral salpingectomy
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- non-hormonal intrauterine device or Mirena® (other hormonal intrauterine devices will not be allowed) in place for at least 3 months prior to the first dose of the study drug
- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom without spermicide
- female condom without spermicide
- cervical cap without spermicide (as prescribed)
- diaphragm without spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom without spermicide) in addition to a second method of acceptable contraception from check-in until 90 days after the follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- cervical cap without spermicide
- diaphragm without spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a

subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol, local legal and regulatory requirements and with the following:

- General principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the institutional review board (IRB)/human research ethics committee (HREC) by the investigator and reviewed and approved by the IRB/HREC before the study is initiated.

Any protocol amendments will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB/HREC. All correspondence with HREC should be retained in the investigator file. A copy of /IRB/HREC approval should be forwarded to the sponsor.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/EC, and all other applicable local regulations.

Regulatory Authority

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following the discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive in accordance with 21 CFR 312.62(c) or for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed as follows:The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X	X				
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.

4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 hour postdose, ±15 minutes for ECGs and vital sign measurements at 2 hours postdose and ±5 minutes for PK sampling at 2 hours postdose, ±5 minutes for 3 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Summary of Amended Protocol Changes

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive Controlled Study to Investigate the Effects of CBP 307 on the QTC Interval in Healthy Subjects

Protocol Amendment 2 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021
Protocol Amendment 2 Date: 03 August 2021
Protocol Version: 3.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Covance Study Number: 8463245
IND Number: 134585

Sponsor:
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737 Burwood Road
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Hawthorn East, Victoria 3123
Australia

Suzhou Connect Biopharmaceuticals, Ltd.
Science and Technology Park
East R&D Building, 3rd Floor
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Taicang, Jiangsu, 215400
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Study Site:
CMAX
Level 5/18a North Terrace
Adelaide, South Australia 5000
Australia

Sponsor Signatory:
Ping Li, MD

Principal Investigator:
Nicholas Farinola, MBBS

The primary changes in this amendment, along with the rationale for the/each change as appropriate, are:

1. Based on recommendations from the regulatory agency, the protocol was modified to add one oral dose administration of placebo-matched CBP-307 capsule on Day 16 for all subjects. This will allow for the placebo comparisons in the assay sensitivity analysis for Days 1 and 16.
2. To update the protocol to exclude male and female subjects with baseline QT interval corrected for heart rate using Fridericia's method (QTcF) >450 msec.
3. To update the protocol to modify the allowable window for any history or evidence of alcoholism or drug/chemical abuse to within 12 months prior to check-in rather than 2 years.
4. To modify the windows for safety assessments at 2 hours postdose in order to provide additional time for the electrocardiogram (ECG) and vital signs measurements due to the required assessments at this timepoint.
5. To remove the specified order for the safety assessments to allow flexibility when the assessments coincide with the ECG extractions.

Minor changes:

1. To update the company name from "Covance" to "Labcorp" as Covance is re-branding into the parent company Labcorp (applicable only for business units transitioned on or after 25 Jun 2021).
2. To modify the protocol to include an administrative change in Medical Monitor from Jane Royalty to Sunu Valasseri.
3. The protocol version and date were updated throughout the protocol.
4. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below:

Title page and all headers

Previously read:

Covance

Now reads:

Labcorp

Study Identification, Medical Monitor and Statistician, page 4

Previously read:

Sponsor's Medical Contact	Jane Royalty, MD Covance Clinical Research Unit, Inc. 3402 Kinsman Boulevard Madison, Wisconsin 53704 USA Tel: 812-474-5015 Email: jane.royalty@covance.com
Statistician	Wei Xiao, MS Covance Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704 USA

Now reads:

Sponsor's Medical Contact	Sunu Valasseri, MD Labcorp Clinical Research Unit Limited. Maidenhead United Kingdom Tel: +44 (0) 113 301 3650 Email: S.Valasseri @labcorp.com
Statistician	Wei Xiao, MS Labcorp Drug Development Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704 USA

Synopsis and Section 3.1, Study Design, paragraph 7

Previously read:

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample

collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

Now reads:

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

Section 4.1 Inclusion Criteria, Criterion #6b

Previously read:

6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    - Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive);
    - QTcF interval ≤450 msec for males and ≤470 msec for females;

- QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
- PR interval ≤200 msec.

Now reads:

6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.

Section 4.2 Exclusion Criteria, Criterion #9

Previously read:

9. History or evidence of alcoholism or drug/chemical abuse within 2 years prior to check-in.

Now reads:

9. History or evidence of alcoholism or drug/chemical abuse within 12 months prior to check-in.

Section 5.1 Investigational Products, Table 3 Study Treatments

Previously read:

Study Treatment Name	**Treatment Group**	**CBP-307**	**CBP-307 Matched Placebo**	**Moxifloxacin (Avelox[2])**	**Moxifloxacin Matched Placebo**
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1				1 tablet
	Group 2A				1 tablet
	Group 2B			1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

Now reads:

Study Treatment Name	**Treatment Group**	**CBP-307**	**CBP-307 Matched Placebo**	**Moxifloxacin (Avelox[2])**	**Moxifloxacin Matched Placebo**
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1		1 capsule		1 tablet
	Group 2A		1 capsule		1 tablet
	Group 2B		1 capsule	1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.

Study Treatment Name	**Treatment Group**	**CBP-307**	**CBP-307 Matched Placebo**	**Moxifloxacin (Avelox[2])**	**Moxifloxacin Matched Placebo**
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

Appendix 6, Schedule of Assessments, CBP-307/Placebo Administration

Previously read:

Schedule of Assessments														
Study Period	**Screening**	**In-house Treatment Period**												**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
CBP-307/placebo administration			X	X	X	X	X	X	X					

Now reads:

Schedule of Assessments														
Study Period	**Screening**	**In-house Treatment Period**												**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
CBP-307/placebo administration			X	X	X	X	X	X	X	X				

Appendix 6, Footnote #5

Previously read:

5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. When timepoints for ECG extraction, safety ECGs, vital signs assessment, and blood draws coincide, procedures will be performed in this order. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.

Now reads:

5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.

Appendix 6, Footnote #8

Previously read:

8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.

Now reads:

8 Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 hour postdose, ±15 minutes for ECGs and vital sign measurements at 2 hours postdose and ±5 minutes for PK sampling at 2 hours postdose, ±5 minutes for 3 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.

Protocol

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 2 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021
Protocol Amendment 2 Date: 03 August 2021
Protocol Version: 3.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Labcorp Study Number: 8463245
IND Number: 134585

Sponsor:
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Suzhou Connect Biopharmaceuticals, Ltd.
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Study Site:
CMAX
Level 5/18a North Terrace
Adelaide, South Australia 5000
Australia

Sponsor Signatory:
Ping Li, MD

Principal Investigator:
Nicholas Farinola, MBBS

SPONSOR APPROVAL

I have read the protocol and approve it:

DocuSigned by:
Pauline Li
签名者名称： Pauline Li
签名原因： 我批准此文档
签名时间： 03 8月 2021 | 10:15:35 下午 PDT
4C556BD566CD4EA4B8EDA87ED35D596

Ping Li, MD Date
VP, Clinical Development Asia

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

DocuSigned by:
Signer Name: Nicholas Farinola
Signing Reason: I approve this document
Signing Time: 04 Aug 2021 | 5:23:05 PM PDT
41E77C67C07F4FF8811CE7A5D4536EB8

Nicholas Farinola, MBBS Date
Principal Investigator

STUDY IDENTIFICATION

Sponsor	Connect Biopharma Australia Pty Ltd. 737 Burwood Road Suite 312 Hawthorn East, Victoria 3123 Australia Suzhou Connect Biopharmaceuticals, Ltd. Science and Technology Park East R&D Building, 3rd Floor 6 Beijing West Road Taicang, Jiangsu 215400 China
Sponsor's Study Contact	Max Meng, BS Project Manager Connect Biopharma Australia Pty Ltd. 737 Burwood Road Suite 312 Hawthorn East, Victoria 3123 Australia Tel: +86 0512 5357 7866 Email: yhmeng@connectpharm.com
Sponsor's Medical Contact	Suni Valasseri, MD Labcorp Clinical Research Unit Limited. Maidenhead United Kingdom Tel: +44 (0) 113 301 3650 Email: S.Valasseri @labcorp.com
Study Site	CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia
Principal Investigator	Nicholas Farinola, MBBS CMAX Level 5/18a North Terrace Adelaide, South Australia 5000 Australia Tel: (08) 7088 7900 Email: nicholas.farinola@sa.gov.au
Clinical Laboratory	Australian Clinical Laboratories 1 Butler Boulevard Adelaide Airport Adelaide, South Australia 5950 Australia

Bioanalytical Laboratory	Peter Tapley Director, TetraQ The University of Queensland Level 7, Block 6, RBWH Herston, Queensland 4029 Australia
Statistician	Wei Xiao, MS Labcorp Drug Development, Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704 USA

SYNOPSIS

Study Title

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the pharmacokinetics (PK) of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on heart rate (HR), PR and QRS intervals, and T-wave morphology.

Study Design

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on

Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a

supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Number of Subjects

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 titrated to 0.1 mg on Day 2; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)
- Moxifloxacin (400 mg; oral tablet).

Duration of Subject Participation in the Study

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 21 days for the in-house treatment period (Days -2 to 19), and 10 ±2 days for follow-up (Day 29±2 days), in total approximately 59 days.

Endpoints

Electrocardiogram (Cardiodynamic):

The primary cardiodynamic endpoint is the change-from-baseline QTcF (ΔQTcF).

The secondary cardiodynamic endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);
- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CBP-307. The PK parameters of CBP-307 will be calculated using a model independent approach. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}), and time of the maximum observed concentration (t_{max}). Other noncompartmental parameters may be reported.

Safety:

Adverse events, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12lead ECGs, and vital signs measurements.

Statistical Methods

Cardiodynamic evaluation:

The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of CBP-307 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma levels. Placebo-corrected ΔHR, ΔPR, ΔQRS, and ΔQTcF (ΔΔHR, ΔΔPR, ΔΔQRS, and ΔΔQTcF) will also be evaluated at each postdosing timepoint ('by-timepoint'

analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.

Pharmacokinetics:

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by cohort. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

Pharmacokinetic/electrocardiography analyses:

The relationship between CBP-307 plasma concentrations and the change from ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12lead ECGs, vital signs, and physical examination findings will be listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CRO	contract research organization
CYP	cytochrome P450
Δ	change-from-baseline
ΔΔ	placebo-corrected or placebo-adjusted change-from-baseline
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HR	heart rate
HREC	human resource ethics committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
LOESS	locally estimated scatterplot smoothing
LS	least squares
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
QD	once daily
QTc	heart-corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method
R_{ac}	accumulation ratio
$R_{ac}(C_{max})$	accumulation ratio for C_{max}

$R_{ac}(AUC_{0-24})$	accumulation ratio for AUC_{0-24}
SAE	serious adverse event
SD	standard deviation
SE	standard error
S1P1	sphingosine-1-phosphate receptor 1
TEAE	treatment-emergent adverse event(s)
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
TQT	thorough QT
V_z/F	apparent volume of distribution
WBC	white blood cell
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the investigator's brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Disease Background

Autoimmune diseases are serious disorders that afflict a large portion of the world population; most have no cures. Significant advances have been made in the development of novel and disease-modifying therapies, but many of these new treatments have significant side effects. Treatments are needed that provide better risk-to-benefit profiles than the existing therapeutic choices.

T cells are important immune cells that mediate the development of autoimmune disorders. Migration of T cells from lymphoid tissues to the sites of inflammation is central to the functions of T cells, and this process is dependent on sphingosine-1-phosphate (S1P) receptor 1 (S1P1) which is known to ameliorate a variety of autoimmune diseases in animals and humans. Down modulation of this receptor, using S1P1 agonists, prevents T cell egress and results in a reduced number of circulating lymphocytes, particularly the CD4+- and CD8+-naïve and central-memory T cell subsets.

1.2. Overview of CBP-307

CBP-307 is an S1P1 agonist that is being developed as a treatment for autoimmune diseases by Suzhou Connect Biopharmaceuticals, Ltd. CBP-307 (1-(2-fluoro-4-(5-(4-isobutylphenyl)-1,2,4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid hemihydrate) is a potent, selective, small-molecule agonist of S1P1 and S1P5 receptors. Cell-based assays have confirmed CBP-307 induces internalization of S1P1 from the cell surface. This is consistent with the known mechanism of action of other S1P1 agonists, in that they down-modulate S1P1 and inhibit lymphocyte egress from lymphoid tissues.

1.2.1. Summary of Clinical Experience

The Phase 1 development of CBP-307 comprised 2 completed studies in healthy subjects:

- A single and multiple ascending dose study to evaluate the safety and tolerability of CBP-307 including pharmacokinetic (PK), pharmacodynamic (PD), and food-effect assessments (Study CBP-307AU001)
- A single-dose and multiple-dose, and fixed-dose titration study to evaluate the safety and tolerability of CBP-307 including PK and PD (Study CBP-307CN001)

Currently, CBP-307 is being evaluated in 2 Phase 2 studies:

- Ongoing multicenter study in subjects with moderate to severe ulcerative colitis (Study CBP-307CN002) to compare the clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing

achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

- Ongoing study in subjects with moderate to severe Crohn's disease compares clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

1.2.1.1. Safety

Study CBP-307AU001

A total of 44 healthy subjects were enrolled in the study. There were 28 subjects evaluated using the single-dose regimen (0.1, 0.25, 0.5, and 2.5 mg CBP-307) of which 21 subjects received CBP-307 and 7 subjects received placebo. Another 16 healthy subjects were evaluated using the multiple-dose regimen (0.15 and 0.25 mg CBP-307 given once daily [QD] for 28 consecutive days) of which 12 subjects received CBP-307 and 4 subjects received placebo.

Overall, no unexpected safety signals were identified and no deaths occurred in this study. For the single-dose regiment, no subjects were discontinued due to a treatment-emergent AE (TEAE). In the multiple-dose regimen, there were 2 subjects who were discontinued from the study (due to increased alanine transaminase and second degree AV block [not considered to be clinically significant, as judged by the investigator]). All TEAEs resolved by the end of the study.

In the single-dose regimen groups, TEAEs were reported in 12 of 21 subjects (57.1%) treated with CBP-307 and in 3 of 7 subjects (42.8%) treated with placebo. Most (91.7%) of the TEAEs in these subjects were mild in severity. The most common TEAEs in the CBP-307-treated groups were headache (28.6%); dizziness (19.0%); and bradycardia (9.5%). Bradycardia was reported only in 2 subjects receiving the highest (2.5 mg) CBP-307 dose. One subject had a serious adverse event (SAE) of bradycardia (associated with transient asystole) following a single dose of 2.5 mg CBP-307.

In the multiple-dose regimen groups, CBP-307 at doses of 0.15 and 0.25 mg QD was generally well tolerated over the 28 days of dosing. Treatment-emergent AEs were reported in 11 of 12 subjects (91.7%) in the CBP-307 groups and 2 of 4 subjects (50.0%) in the placebo groups. Most (83.3%) TEAEs were mild in severity. The most common TEAEs in the 2 CBP-307 groups were headache (50.0%), and fatigue, nausea, and musculoskeletal pain (16.7% each). The incidences of these TEAEs were similar in both CBP-307-treated groups. No SAEs were reported for subjects in the multiple-dose regimen.

Study CBP-307CN001

A total of 30 eligible subjects completed 3 CBP-307 dose groups in ascending order of dose after randomization (in a ratio of 1:1:1): Group A (0.1 mg), Group B (0.2 mg), and Group C (0.3 mg). Each dose group consisted of 10 subjects, including 8 subjects receiving the investigational drug and 2 subjects receiving placebo by random assignment. The administration started from the dose of 0.1 mg. The subjects in this group received a single

dose of CBP-307 or placebo and were followed up for safety and tolerance within the next 7 days. Then the subjects received 0.1 mg CBP-307 or placebo QD for 14 consecutive days and were followed up for safety and tolerance within the next 7 days. Dose escalation did not occur until the review of the single-dose regimen safety data from the 6 subjects in the previous dose cohort, and the safety data did not meet the termination criteria. The subjects in the dose of 0.3 mg received fixed-dose titration regimen, ie, 0.05 mg CBP-307 or placebo QD for 3 consecutive days; 0.1 mg CBP-307 or placebo QD for 2 consecutive days; 0.2 mg CBP-307 or placebo QD for 2 consecutive days; finally, 0.3 mg CBP-307 or placebo QD for 14 consecutive days, and the subjects were followed up for safety and tolerance within the next 7 days.

Overall, no unexpected safety signals were identified, and there were no deaths, SAEs, or AEs leading to the subject's early withdrawal from the study after administration of CBP-307. In the safety set, a total of 29 subjects (8 in Group A, 100%; 8 in Group B, 100%; 8 in Group C, 100% and 5 in placebo group, 83.3%) experienced TEAEs.

During the single-dose period, a total of 14 subjects (5 of 8 in Group A, 62.5%; 6 of 8 in Group B, 75%, and 3 of 4 in placebo group, 75%) developed AEs. The incidence of TEAEs in Group A was generally similar to the placebo group. Among TEAEs in Group B, the incidence of AEs related to abnormalities in investigations was higher than that in placebo group, including lymphocyte count decreased (12.5%), white blood cell (WBC) count decreased (12.5%), neutrophil count decreased (12.5%), alanine aminotransferase increased (25%), and gamma-glutamyltransferase increased (12.5%), and aspartate aminotransferase increased (12.5%). Additionally, 1 subject experienced heart rate (HR) decreased (12.5%).

During dose-titration period, 2 subjects (2 of 8 in Group C, 25%) experienced TEAEs. The TEAEs reported in Group C during the titration period included cough (12.5%) and increased upper airway secretion (12.5%). There were no TEAEs in the placebo group during this period.

During repeated-dose period, a total of 28 subjects (8 of 8 in Group A, 100%; 8 of 8 in Group B, 100%; 8 of 8 in Group C, 100%; and 4 of 6 in placebo group, 66.7%) experienced AEs. The most frequent TEAE in Group A was upper respiratory tract infection (37.5%) compared with placebo group; the most frequent TEAEs in Group B and Group C included decreased lymphocyte count (Group B, 87.5%; Group C, 100.0%), WBC count (Group B, 87.5%; Group C, 62.5%), and neutrophil count (Group B, 50%; Group C, 12.5%). The TEAEs noted in Group B during the repeated-dose period also included increased alanine aminotransferase (25%), gamma-glutamyltransferase (37.5%), and aspartate aminotransferase (12.5%), upper respiratory tract infection (12.5%), influenza (12.5%), chest pain (12.5%), lethargy (25%), and neck pain (12.5%); TEAEs in Group C during the repeated-dose period also included increased alanine aminotransferase (25%), decreased HR (12.5%), and mouth ulcer (12.5%); the TEAEs in placebo group included increased transaminase (16.7%), prolonged activated partial thromboplastin time (1/6, 16.7%), decreased hemoglobin (16.7%), upper respiratory tract infection (16.7%), diarrhea (16.7%), dizziness (16.7%), and palpitations (16.7%).

Study CBP-307CN002

This study is ongoing and there are no safety data available.

Study CBP-307CN003

This study is ongoing and there are no safety data available.

1.2.1.2. Pharmacokinetics

CBP-307 given orally as a single dose was readily absorbed; drug concentrations peaked at approximately 6 hours after administration, with an elimination apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours (range of 23 to 29 hours). The time to maximum observed concentration (C_{max}) in the blood was delayed from 6 hours to approximately 10 hours when CBP-307 was given with a high-fat diet. Food consumption also increased exposure (Table 1).

For the single-dose administration, CBP-307 exposure (based on C_{max} and area under the concentration-time curve [AUCs]) increased with increasing dose following a single-dose administration (Table 1).

Table 1: Pharmacokinetics Parameters in the Single-Dose CBP-307 Regimen (Study CBP-307AU001)

Single-Dose Regimen PK Parameters	Mean CBP-307 Single Dose ± SEM (n)				
	0.1 mg	**0.25 mg**	**0.5 mg (fasted)**	**0.5 mg (fed)[a]**	**2.5 mg**
AUC_{last} (ng*h/mL)	13.4 ± 3.54 (n = 6)	45.1 ± 5.25 (n = 6)	160 ± 22.8 (n = 6)	290 ± 28.1 (n = 6)	550 ± 96.3 (n = 3)
AUC_{inf} (ng*h/mL)	ND	63.7 ± 2.14 (n = 3)	214 ± 58.3 (n = 3)	355 ± 44.3 (n = 5)	710 ± 164 (n = 2)
C_{max} (ng/mL)	0.537 ± 0.0931 (n = 6)	1.53 ± 0.0935 (n = 6)	4.84 ± 0.706 (n = 6)	8.58 ± 1.11 (n = 6)	19.0 ± 3.55 (n = 3)
t_{max} (hours)	7.33 ± 1.33 (n = 6)	5.33 ± 0.99 (n = 6)	5.00 ± 0.86 (n = 6)	10.67 ± 2.72 (n = 6)	6.00 ± 2.00 (n = 3)
$t_{1/2}$ (hours)	ND	23.3 ± 1.70 (n = 3)	28.8 ± 1.28 (n = 3)	26.0 ± 1.17 (n = 5)	22.8 ± 3.96 (n = 2)

Abbreviations: AUC_{inf} = area under the curve at infinity; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; h = hour(s); mg = milligram(s); ND = not determinable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SEM = standard error of the mean; $T_{1/2}$ = elimination half-life; T_{max} = time to maximum concentration.
[a] Study Part 1b: Cohort 3 from Part 1a returned to receive a single oral dose of CBP-307 at 0.5 mg under fed conditions.
Source: Final report for Study CBP-307AU001.

For the repeated-dose administration of CBP-307, the C_{max} and AUCs increased with the higher administered dose (Table 2). At the steady-state timepoint on Day 28, the median CBP-307 t_{max} was 4 to 6 hours. The average $t_{1/2}$ was similar, ranging 44 to 49 hours, and there were no dose-dependent changes in $t_{1/2}$ within the dose range. The $t_{1/2}$ was slightly prolonged after repeated-dose administration when compared with that after a single-dose administration. Moderate accumulation of CBP-307 (approximately 3 times the levels

following a single dose) was noted in plasma after QD administration for 14 consecutive days.

Table 2: Pharmacokinetics Parameters in the Multiple-Dose CBP-307 Regimen (Study CBP-307AU001)

Multiple-Dose Regimen PK Parameters	Multiple-Dose Cohort 1 CBP-307 Dosing, mg (± SD) (n)		Multiple-Dose Cohort 2 CBP-307 Dosing, mg (± SD) (n)	
	Day 1 0.1	Day 28 0.25	Day 1 0.15	Day 28 0.15
AUC_{0-24} (ng*h/mL)	24.5 ± 3.26 (n = 5)	125 ± 12.4 (n = 4)	26.3 ± 7.45 (n = 5)	79.7 ± 27.3 (n = 6)
AUC_{last} (ng*h/mL)	NA	203 ± 21.9 (n = 4)	NA	131 ± 44.7 (n = 6)
C_{max} (ng/mL)	1.45 ± 0.214 (n = 5)	6.30 ± 0.588 (n = 4)	1.32 ± 0.422 (n = 6)	4.23 ± 1.45 (n = 6)
t_{max} (hours)	6.80 ± 1.50 (n = 5)	6.50 ± 1.50 (n = 4)	5.00 ± 0.68 (n = 6)	4.33 ± 0.33 (n = 6)

Abbreviations: AUC_{0-24} = area under the curve from time 0 to 24 hours; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; mg = milligram(s); NA = not applicable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SD = standard deviation; T_{max} = time to maximum concentration.
Source: Final report for Study CBP-307AU001.

1.3. Overview of Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of International Council for/Conference on Harmonisation (ICH) E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[2]

1.4. Study Rationale

Regulatory guidance (ICH E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase 1, 2, and 3 trials may be conducted they usually have an insufficient sample size, infrequent sampling of ECG data, or the use of inadequate controls to overcome the high rate of spontaneous change in QTc duration. This has resulted in regulatory guidance recommending a dedicated or thorough trial to define the ECG effects of new drugs.

This study will be done in healthy subjects to eliminate variables known to have an effect on ECG parameters (concomitant drugs, diseases, etc.). A supratherapeutic dose of CBP-307 is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (eg, concomitant use of cytochrome P450 [CYP]3A4

inhibitor, concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to allow for PK to QTc modeling to assess the effect of drug concentration on cardiac repolarization.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with CBP-307 may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the PK of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on HR, PR and QRS intervals, and T-wave morphology.

2.2. Endpoints

2.2.1. Electrocardiogram Endpoints

2.2.1.1. Primary

The primary endpoint is the change-from-baseline QTcF (ΔQTcF).

2.2.1.2. Secondary

The secondary endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);

- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

2.2.2. Pharmacokinetic Endpoints

Pharmacokinetic parameters of CBP-307 will be determined if data allows:

- area under the concentration‑time curve from time zero extrapolated to infinity (AUC_{inf})
- area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})

Other PK parameters may also be reported.

2.2.3. Safety Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether

volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

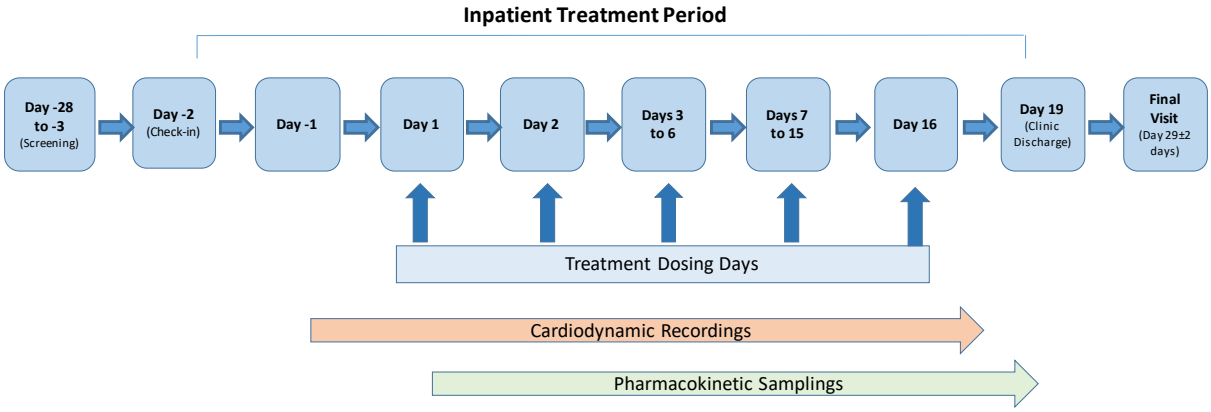
The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Day 2, Days 3 to 6, Days 7 to 15, and Day 16. Dosing details are provided in Table 3. Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. An end-of-study visit will occur on Day 29±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for CBP-307 to cause QT prolongation. As CBP-307 exposure affects heart rate, the primary endpoint for this study will be the QTcF.

The study will be randomized and double-blind because randomization eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions, thus eliminating the possibility that the observed effects of the intervention are because of differential use of other treatments.

The sample size for this study is based on a formal statistical power calculation.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Both male and female subjects will be included to eliminate similar known ECG variability effects.

Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Pharmacokinetic assessments of CBP-307 concentrations in plasma will be evaluated during the study. The timepoints for the PK sample collections are based on previous studies and are considered adequate to allow for the characterization of the drug's PK after oral dosing. Furthermore, the chosen PK sample collection for CBP-307 is anticipated to be sufficient to allow reasonable estimation of $t_{1/2}$ during the terminal elimination phase.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.05 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2 and a dose of 0.2 mg on Days 3 to 6. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index between 18.0 and 30.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and confirmed at check-in as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4. Negative pregnancy test for females of childbearing potential at screening (blood test) and check-in (urine test).
5. Supine diastolic blood pressure between 60 and 90 mmHg and systolic blood pressure between 90 and 140 mmHg (inclusive) at screening on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest.
6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.
7. Has serum potassium, calcium, and magnesium levels within the normal reference range at screening, as judged by the investigator.
8. Able to swallow multiple tablets (based on subject's verbal confirmation).
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Subject is mentally or legally incapacitated or has had significant history of recent mental health issues requiring medication and/or hospitalization at the time of the screening visit or expected during the conduct of the study.

2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee). *Note: Childhood asthma that is considered recovered or seasonal allergies that are not currently active or requiring treatment are allowed.*
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
4. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
5. History of significant multiple and/or severe allergies (eg, latex allergy, band-aids, adhesive dressing, or medical tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.
6. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs within 6 months prior to the first dose of study drug (uncomplicated appendectomy and hernia repair will be allowed).
7. History or presence of:
    a. Hypokalemia, in the opinion of the investigator (or designee);
    b. Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
    c. Sick sinus syndrome, second, or third degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities;
    d. Repeated or frequent syncope or vasovagal episodes;
    e. Hypertension, angina, bradycardia, or severe peripheral arterial circulatory disorders.
8. Clinically significant abnormalities (as judged by the investigator in laboratory tests results [out-of-range results confirmed on repeat]), including but not limited to the following parameters:
    a. alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin greater than 1.5 × upper limit of normal;
    b. hemoglobin <10 g/dL, WBC <3.0 $\times 10^9$/L, neutrophils <1.5 $\times 10^9$/L, lymphocytes <0.8 $\times 10^9$/L and platelets <100 $\times 10^9$/L or >1200 $\times$ 10^9/L;
9. History or evidence of alcoholism or drug/chemical abuse within 12 months prior to check-in.
10. Alcohol consumption of >10 units per week for males and females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
11. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.

12. Positive hepatitis panel, positive syphilis test, and/or positive human immunodeficiency virus test (Appendix 2).
13. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 28 days prior to the first dose of study treatment on Day 1. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
14. Participation in a previous clinical study where subjects received CBP-307.
15. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 28 days prior to first dose of study treatment on Day 1.
16. Use or intend to use any prescription medications/products within 14 days prior to first dose of study drug (Day 1) and throughout the study, unless deemed acceptable by the investigator (or designee). *Note: For females only, the use hormonal contraception, hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives within 14 days prior to Day 1 is not acceptable, except for Mirena®.*
17. Use or intend to use any drugs known to be significant inhibitors or inducers of CYP enzymes and/or P-gp, including St. John's Wort, for days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the investigator or designee to confirm the lack of PK/PD interaction with the study drug.
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intend to use any nonprescription medications/products including antacids, vitamins (especially those containing magnesium, aluminum, iron, or zinc), minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
21. Has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for whatever reason), in the opinion of the investigator, within the 28 days prior to the first dose of study treatment, and throughout the study.
22. Consumption of caffeine/xanthine-containing foods or beverages within 48 hours prior to check-in until discharge.
23. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
24. Receipt of blood products within 2 months prior to check-in.
25. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
26. Poor peripheral venous access.

27. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Eligible subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). The screening number will be used on all safety samples throughout the study. Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw their informed consent from the study at any time or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, or the inability of the subject to comply with the protocol-required visits or procedures. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- investigator decides to terminate the study due to safety concerns such as AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development
- sponsor requests for termination (eg, due to financial or management reasons, etc.) under the premise to fully protect the safety and rights of subjects
- health authority or ethics committee (EC) orders the termination of the trial for any reason.

Definition of end-of-treatment and end-of-study

- end-of-treatment is completion of safety follow-up or withdrawal from the study. End-of-study is the last visit by the last subject.

5. STUDY TREATMENTS

Study treatments are defined as any investigational product (IP), non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as IMP and non-IMP, respectively.

5.1. Investigational Products

The details regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 will be provided in a separate document. Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Table 3: Study Treatments

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1		1 capsule		1 tablet
	Group 2A		1 capsule		1 tablet
	Group 2B		1 capsule	1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

All supplies of the IMP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study treatments will be stored at the study site in a location that is locked with restricted access.

5.2. Study Treatment Administration

Each dose of study treatment (CBP-307, placebo, or moxifloxacin) will be administered orally following an overnight fast of at least 10 hours, with approximately 240 mL of room temperature water. Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Subjects will be dosed in numerical order while sitting or standing but not be permitted to lie supine for 2 hours after treatment administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a double-blind randomized study. Subjects will be randomized to one of the treatment sequences before administration of the first dose of study treatment. A randomization list will be generated by a statistician using a computer-generated pseudo-random permutation procedure. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the study site. Randomization details will be included in the randomization specification.

5.4. Blinding

This is a double-blinded study. The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to CBP-307 or moxifloxacin.
- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.
- Interim bioanalytical data will be provided to Labcorp Early Clinical Biometrics in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing coded details of the treatment. These individually sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until the completion of the study.

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy (RAH Pharmacy), per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from the use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the investigator (or designee) and/or sponsor have given their prior consent. Medications taken within 28 days before study treatment administration will be documented as a prior treatment. Treatments taken after study treatment administration will be documented as concomitant treatments.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for the treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Females will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives (with the exception of Mirena®) during the study until the follow-up visit (Appendix 4).

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 29±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 19.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 19 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 29±2 days.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until the follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 29±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

This study includes a screening period (Day -28 to Day -3), a treatment period (Days -2 to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

7.1. General Assessments

7.1.1. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.1.2. Medical History

At the timepoint specified in Appendix 6, the investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

Continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. All ECG data will be collected using a Holter (or Mortara Surveyor) ECG continuous 12-lead digital recorder. The 12-lead Holter (or Mortara Surveyor) ECG equipment will be supplied and supported by ERT (eResearch Technology Inc., Philadelphia, PA). The continuous 12-lead digital ECG data will be stored onto SD memory cards.

The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT (eResearch Technology Inc., Philadelphia, PA). The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints and subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter (or Mortara Surveyor) recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically,

the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position).

7.2.1.2. Expert Precision QT Analysis

Expert precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc, or RR from beat-to-beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR values from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS interval of the ECG (QRS) intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed (ie, changes not present at baseline). For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline.

7.2.2. Safety 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria applies:

- QT interval corrected for HR using Fridericia's method (QTcF) is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.3. Cardiac Telemetry Monitoring

Subjects will be monitored via cardiac telemetry from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days; as described in Appendix 6). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary.

The start and stop date and time of the telemetry monitoring will be recorded in the eCRFs. Clinically significant abnormalities noted from telemetry monitoring will be confirmed by 12-lead ECG if necessary, then after confirming, the abnormities will be reported as AEs in the eCRF.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 × 3 mL for CBP-307 and moxifloxacin assays) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of CBP-307 and moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the follow-up visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of placebo administration to all subjects (Day -1) until study completion. If AEs that occur in the screening prior to placebo administration to all subjects (Day -1) are considered to be related to the study procedure, they should be also collected. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator’s (or designee’s) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

A serum qualitative pregnancy or urine test (females only) and follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test. All pregnancies should be reported as specified in Appendix 1.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. At the discretion of the investigator, clinically significant clinical laboratory assessments may be confirmed by repeat sampling. If the clinical significance is confirmed, subjects will be excluded from participation or, if already included, will be followed until normalization of the test result or for as long as the investigator considers necessary.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.4.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and tympanic temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Physical examinations include general appearance, head, eyes,

ears, nose, and throat, neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, skin, and others.

Height, weight, and body mass index will be assessed at screening.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Sample Size for Primary Analysis:

A sample size of 28 evaluable subjects per treatment group will provide more than 94.4% power to exclude that CBP-307 causes more than 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QT effect (ΔΔQTcF) at the observed geometric mean C_{max} of CBP-307 in the study. This power is estimated approximately using a 2-sample t-test. The calculation assumes a 1-sided 5% significance level, an underlying effect of CBP-307 of 3 msec and a standard deviation (SD) of the ΔQTcF of 8 msec for both CBP-307 and placebo treatment groups. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed-effects model. The concentration-QTc analysis method is supported by Darpo et al 2015[3] and Ferber et al, 2015,[4] and consistent with the experiences from 25 recent TQT studies.

Sample Size Considerations for Assay Sensitivity:
To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.64 required to guarantee a power of at least 95% in a paired t-test situation with a sample size of 28 evaluable subjects. In other words, based on this calculation, a power of at least 95% will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD from the by-timepoint analysis, does not exceed 6.9 msec (ie, 128% [= 0.82/0.64] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects.[5]

8.2. Analysis Populations

8.2.1. Cardiodynamic Population

The QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value. The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

The PK/QTc population will include all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for CBP-307, and for moxifloxacin.

The as-treated principle will be applied to all analysis populations mentioned below.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of investigational product and have evaluable PK data of any of the analytes (CBP-307 and moxifloxacin). A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of investigational product drug (therapeutic and supratherapeutic doses of CBP-307, moxifloxacin, or placebo).

8.3. Cardiodynamic ECG Analyses

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 16, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 16, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 15.

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6]

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 6, and 15, and Days 1 and 16 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 6 and 15 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 6 and 15 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max}

<10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 6 and 15; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 6 and 15; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 6 and 15, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and

time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

8.4. Pharmacokinetic Analyses

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, SD, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by group. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_Z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)
- Accumulation ratio (R_{ac}) for C_{max} ($R_{ac[Cmax]}$) and $R_{ac(AUC0-24)}$, calculated as Day 15 C_{max}/Day 7 C_{max} and Day 15 AUC_{0-24}/Day 7 AUC_{0-24}, respectively.

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Other parameters may be added as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the Statistical Analysis Plan.

8.5. Safety Analysis

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

8.6. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication.

Examples of AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving clinically significant abnormal laboratory tests, ECG, etc.)
- Exacerbation of previous condition, including increased incidence and/or severity.

Note: Regarding decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. All AEs will be recorded in the medical records and eCRFs. The investigator (or designee) is to record in detail any AE that occurred to the subject, including: AE diagnosis whenever possible, or signs, symptoms, the start date and time of occurrence, the stop date and time of occurrence, seriousness (ie, whether it is an SAE), severity of AEs, causality assessment, actions taken on the investigational product, other actions (eg, medications/treatments given), and outcomes of AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: 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, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

All SAEs will be collected after subjects sign the informed consent form and throughout the entire study, ie, until the end-of-study as specified in the protocol (or at early termination).

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor (or designee).

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp APAC Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to: +61-2-8879-2000

SAE Reporting email: SAEIntake@labcorp.com (preferred method)

Labcorp Safety SAE Reporting Fax Number: 61-2-6100-9788 or 1800-882-203 (toll free)

The responsibilities of Labcorp APAC Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp APAC Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the EC, Medicines and Healthcare Products Regulatory Agency, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

For SAEs, the active reporting period to sponsor or its designated representative begins from the time that the subject provides informed consent through to the last subject visit.

Nonserious AEs should be collected from the time the subject has taken the placebo dose on Day -1 through the last subject visit. If AEs that occur in the screening prior to the placebo administration to all subjects on Day -1 are considered to be related to the study procedure, they should be also collected.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, the sponsor should be notified within 24 hours of investigator awareness of the event. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting as specified above. In addition, an investigator

may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

If the female subject becomes pregnant during the clinical trial and has not yet been dosed with study treatment, she must be withdrawn from the study. If the female subject becomes pregnant during the clinical trial and has been dosed, she must discontinue treatment immediately but may remain on study for safety evaluations. If the partner of a male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should report to the sponsor or designee in a pregnancy report form within 24 hours after investigator awareness and report to the EC in time as per local requirement.

The investigator will follow up on pregnancy outcomes, until not less than 12 months after birth, unless otherwise justified, and will report the outcome to the sponsor and ethics committee.

If any adverse pregnancy outcome (eg, the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformations), it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if indicated by dipstick)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen Syphilis	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol Tricyclic antidepressants Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b] **Other Tests** Low density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	41	328
Total:			390.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the follow-up visit. Primary (non-barrier) methods of contraception include:

- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation or bilateral salpingectomy
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- non-hormonal intrauterine device or Mirena® (other hormonal intrauterine devices will not be allowed) in place for at least 3 months prior to the first dose of the study drug
- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom without spermicide
- female condom without spermicide
- cervical cap without spermicide (as prescribed)
- diaphragm without spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom without spermicide) in addition to a second method of acceptable contraception from check-in until 90 days after the follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- cervical cap without spermicide
- diaphragm without spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a

subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol, local legal and regulatory requirements and with the following:

- General principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the human research ethics committee (HREC) by the investigator and reviewed and approved by the HREC before the study is initiated.

Any protocol amendments will require EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the HREC. All correspondence with HREC should be retained in the investigator file. A copy of HREC approval should be forwarded to the sponsor.

- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of SAEs or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the EC, and all other applicable local regulations.

Regulatory Authority

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following the discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed as follows:The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X	X				
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.

4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 hour postdose, ±15 minutes for ECGs and vital sign measurements at 2 hours postdose and ±5 minutes for PK sampling at 2 hours postdose, ±5 minutes for 3 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Summary of Amended Protocol Changes

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Amendment 1 Status: Final
Original Protocol Date: 18 March 2021
Protocol Amendment 1 Date: 10 May 2021

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Covance Study Number: 8463245
IND Number**:** 134585

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Principal Investigator:
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The primary changes in this amendment, along with the rationale for the/each change as appropriate, are:

1. Update the protocol to add a new CBP-307 dose group (0.05 mg) in the up-titration period.
2. Update the applicable assessment timepoints throughout the protocol to align with the additional dose group added in the up-titration period.
3. Update the protocol to include additional pharmacokinetic (PK) sample collections at 72 and 96 hours after the final CBP-307 dose on Day 15 to better capture the terminal phase PK parameters of CBP-307 after 0.5 mg multiple doses.
4. Update the protocol to include additional PK parameters.
5. Update the protocol to include cardiac telemetry monitoring.

Minor changes:

1. Minor editorial changes have been made.
2. The protocol version and date were updated throughout the protocol.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below:

Synopsis, Study Design

Previously read:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2 to 5, 6 to 14, and on Day 15 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1)
- A therapeutic dose of CBP-307 (0.2 mg, Day 2 to 5)
- A supratherapeutic dose of CBP-307 (0.5 mg, Day 6 to 14)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 16. Treatment administration will occur on Days 1, 2 to 5, 6 to 14, and 15 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 5, 14, and 15 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Subjects will return to the study site for a follow-up visit on Day 28±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 5, 14, and 15. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 14, and 15.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 58 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Now reads:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)

- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during

the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Synopsis, Investigational Medicinal Products, Dose and Mode of Administration

Previously read:

The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Day 2 to 5; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Day 6 to 14; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)
- Moxifloxacin (400 mg; oral tablet).

Now reads:

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 titrated to 0.1 mg on Day 2; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)
- Moxifloxacin (400 mg; oral tablet).

Synopsis, Duration of Study Participation in the Study

Previously read:

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 18 days for the in-house treatment

period (Days -2 to 16), and 12 ±2 days for follow-up (Day 28±2 days), in total approximately 58 days.

Now reads:

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 21 days for the in-house treatment period (Days -2 to 19), and 10 ±2 days for follow-up (Day 29±2 days), in total approximately 59 days.

Section 3.1, Overall Study Design and Plan

Previously read:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2 to 5, 6 to 14, and on Day 15 (placebo will be administered to all subjects on Day -1).

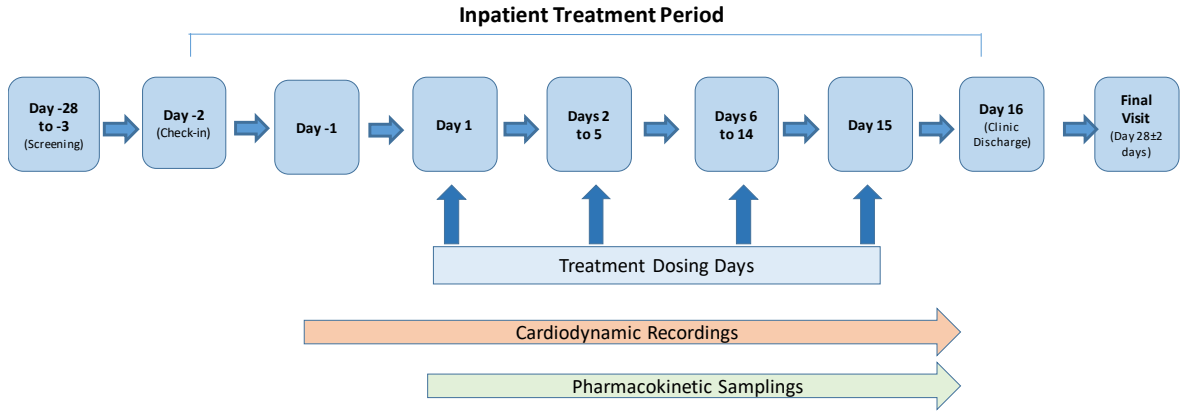
The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1)
- A therapeutic dose of CBP-307 (0.2 mg, Days 2 to 5)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 6 to 14)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Days 2 to 5, Days 6 to 14, and Day 15. Dosing details are provided in Table 3.
Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint.
An end-of-study visit will occur on Day 28±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 16. Treatment administration will occur on Days 1, 2 to 5, 6 to 14, and 15 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 5, 14, and 15 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Subjects will return to the study site for a follow-up visit on Day 28±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 5, 14, and 15. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior

to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 14, and 15.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 58 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

Now reads:

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

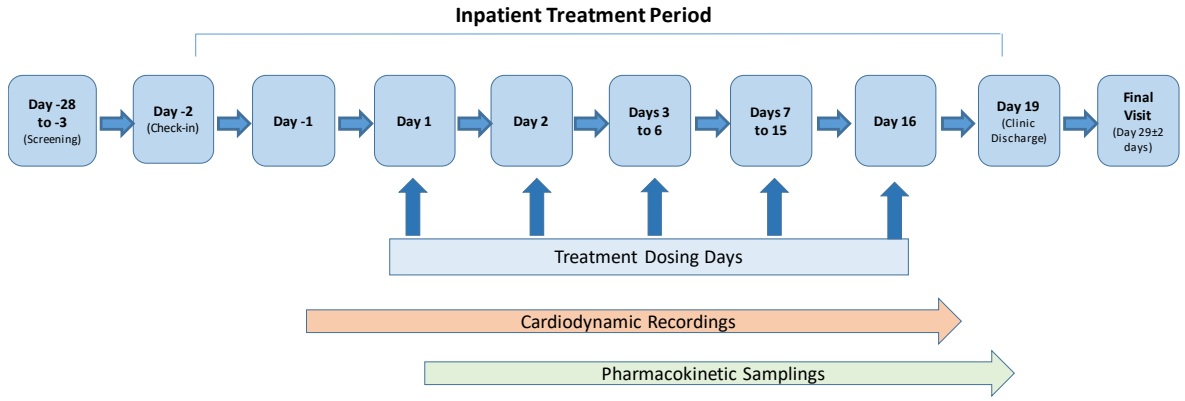
The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Day 2, Days 3 to 6, Days 7 to 15, and Day 16. Dosing details are provided in Table 3. Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. An end-of-study visit will occur on Day 29±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at

each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

Section 3.3, Selection of Doses in the Study

Previously read:

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.1 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.2 mg on Days 2 to 5. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

Now reads:

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.05 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2 and a dose of 0.2 mg on Days 3 to 6. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

Section 5.1, Investigational Products, Table 3

Previously read:

Study Treatment Name	**Treatment Group**	**CBP-307**	**CBP-307 Matched Placebo**	**Moxifloxacin (Avelox[2])**	**Moxifloxacin Matched Placebo**
Dosage Formulation		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.1 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Days 2 to 5	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 6 to 14	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 15	Group 1				1 tablet
	Group 2A				1 tablet
	Group 2B			1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

Now reads:

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1				1 tablet
	Group 2A				1 tablet
	Group 2B			1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of	Treatments will be administered after the completion of all predose procedures and after a fast of	Treatments will be administered after the completion of all predose procedures and after a fast of	Treatments will be administered after the completion of all predose procedures and after a fast of

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
		at least 10 hours with approximately 240 mL of room temperature water.	at least 10 hours with approximately 240 mL of room temperature water.	at least 10 hours with approximately 240 mL of room temperature water.	at least 10 hours with approximately 240 mL of room temperature water.

Section 6.2, Diet

Previously read:

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 28±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 16.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 16 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 28±2 days.

Now reads:

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 29±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 19.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 19 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 29±2 days.

Section 6.4, Exercise

Previously read:

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 28±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

Now reads:

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 29±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

Section 7, Study Assessments and Procedures, paragraph 3

Previously read:

This study includes a screening period (Day -28 to Day -2), a treatment period (Days -1 to 16), and a follow-up period (Day 28 ±2 days).

Now reads:

This study includes a screening period (Day -28 to Day -3), a treatment period (Days -2 to 19), and a follow-up period (Day 29 ±2 days).

Section 7.2.3, Cardiac Telemetry Monitoring

Previously read:

NA

Now reads:

Subjects will be monitored via cardiac telemetry from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days; as described in Appendix 6). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary.

The start and stop date and time of the telemetry monitoring will be recorded in the eCRFs. Clinically significant abnormalities noted from telemetry monitoring will be confirmed by 12 lead ECG if necessary, then after confirming, the abnormalities will be reported as AEs in the eCRF.

Section 8.3, Cardiodynamic ECG Analyses

Previously read:

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 15, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 14 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 15, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 14.

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 5, and 14 categorical) as fixed effects, and a random intercept and slope per subject.[6]

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 5, and 14, and Days 1 and 15 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 5 and 14 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 5 and 14 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max} <10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 5 and 14; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 5 and 14; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 5 and 14, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 5, and 14: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 14, and corresponding placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 5, and 14 at each postbaseline timepoint on Days 1, 5, and Day 14, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 15. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 15: categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

Now reads:

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 16, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 16, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 15.

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6]

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment

effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 6, and 15, and Days 1 and 16 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 6 and 15 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 6 and 15 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max} <10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 6 and 15; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 6

and 15; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 6 and 15, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16:

categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

Section 8.4, Pharmacokinetic Analyses, paragraph 2

Previously read:

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λz)
- $t_{1/2}$

- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

Now reads:

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)
- Accumulation ratio (R_{ac}) for C_{max} ($R_{ac[Cmax]}$) and $R_{ac(AUC0-24)}$, calculated as Day 15 C_{max}/Day 7 C_{max} and Day 15 AUC_{0-24}/Day 7 AUC_{0-24}, respectively.

Appendix 2: Clinical Laboratory Evaluations, Footnote "b"

Previously read:

[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 28±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Now reads:

[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

Previously read:

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	40	320
Total:			382.5

Now reads:

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	41	328
Total:			390.5

Appendix 6: Schedule of Assessments

Previously read:

Schedule of Assessments											
Study Period	**Screening**	**In-house Treatment Period**									**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2 to 4**	**5**	**6 to 13**	**14**	**15**	**16**	**28±2**
Informed consent	X										
Eligibility criteria review (Inclusion/Exclusion)	X	X									
Demographics	X										
Medical history	X										
Admission to clinical research unit[1]		X									
Discharge from clinical research unit[2]										X	
Randomization				X							
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X										
Physical exam	X	X									X
Hematology	X	X				X				X	X
Clinical chemistry (including cholesterol panel tests)	X	X				X				X	X
Urinalysis	X	X								X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X										
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X	X
Breath alcohol, urine drug toxicology and cotinine	X	X									
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X		X		X	X		

Schedule of Assessments

Study Period	Screening	In-house Treatment Period									End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2 to 4**	**5**	**6 to 13**	**14**	**15**	**16**	**28±2**
Pregnancy test[6]	X	X									X
Follicle -stimulating hormone test (postmenopausal females only)	X										
CBP-307/placebo administration			X	X	X	X	X	X			
Moxifloxacin/placebo administration				X					X		
Blood sampling for PK[7,8]				X		X		X	X		
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 24-hour PK samples and after completion of safety assessments on Day 16.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Day 16):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Discharge (Day 16):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 28±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days and before discharge on Day 16. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 5, 14, and 15. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. When timepoints for ECG extraction, safety ECGs, vital signs assessment, and blood draws coincide, procedures will be performed in this order. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 14, and 15.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 28±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15).
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose.

Now reads:

Schedule of Assessments														
Study Period	**Screening**	**In-house Treatment Period**												**End-of-Study/Follow-up Visit**
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						
Breath alcohol, urine drug toxicology and cotinine	X	X												

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X					
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. When timepoints for ECG extraction, safety ECGs, vital signs assessment, and blood draws coincide, procedures will be performed in this order. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus

placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.

6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Protocol

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

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Covance Study Number: 8463245
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INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

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SYNOPSIS

Study Title

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the pharmacokinetics (PK) of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on heart rate (HR), PR and QRS intervals, and T-wave morphology.

Study Design

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on

Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to

10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Number of Subjects

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 titrated to 0.1 mg on Day 2; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)

- Moxifloxacin (400 mg; oral tablet).

Duration of Subject Participation in the Study

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 21 days for the in-house treatment period (Days -2 to 19), and 10 ±2 days for follow-up (Day 29±2 days), in total approximately 59 days.

Endpoints

Electrocardiogram (Cardiodynamic):

The primary cardiodynamic endpoint is the change-from-baseline QTcF (ΔQTcF).

The secondary cardiodynamic endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);
- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CBP-307. The PK parameters of CBP-307 will be calculated using a model independent approach. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}), and time of the maximum observed concentration (t_{max}). Other noncompartmental parameters may be reported.

Safety:

Adverse events, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12lead ECGs, and vital signs measurements.

Statistical Methods

Cardiodynamic evaluation:

The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of CBP-307 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically

relevant plasma levels. Placebo-corrected ΔHR, ΔPR, ΔQRS, and ΔQTcF (ΔΔHR, ΔΔPR, ΔΔQRS, and ΔΔQTcF) will also be evaluated at each postdosing timepoint ('by-timepoint' analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.

Pharmacokinetics:

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by cohort. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

Pharmacokinetic/electrocardiography analyses:

The relationship between CBP-307 plasma concentrations and the change from ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12lead ECGs, vital signs, and physical examination findings will be listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CRO	contract research organization
CYP	cytochrome P450
Δ	change-from-baseline
ΔΔ	placebo-corrected or placebo-adjusted change-from-baseline
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HR	heart rate
HREC	human resource ethics committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
LOESS	locally estimated scatterplot smoothing
LS	least squares
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
QD	once daily
QTc	heart-corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method
R_{ac}	accumulation ratio
$R_{ac}(C_{max})$	accumulation ratio for C_{max}

$R_{ac}(AUC_{0-24})$	accumulation ratio for AUC_{0-24}
SAE	serious adverse event
SD	standard deviation
SE	standard error
S1P1	sphingosine-1-phosphate receptor 1
TEAE	treatment-emergent adverse event(s)
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
TQT	thorough QT
V_z/F	apparent volume of distribution
WBC	white blood cell
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the investigator's brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Disease Background

Autoimmune diseases are serious disorders that afflict a large portion of the world population; most have no cures. Significant advances have been made in the development of novel and disease-modifying therapies, but many of these new treatments have significant side effects. Treatments are needed that provide better risk-to-benefit profiles than the existing therapeutic choices.

T cells are important immune cells that mediate the development of autoimmune disorders. Migration of T cells from lymphoid tissues to the sites of inflammation is central to the functions of T cells, and this process is dependent on sphingosine-1-phosphate (S1P) receptor 1 (S1P1) which is known to ameliorate a variety of autoimmune diseases in animals and humans. Down modulation of this receptor, using S1P1 agonists, prevents T cell egress and results in a reduced number of circulating lymphocytes, particularly the CD4+- and CD8+-naïve and central-memory T cell subsets.

1.2. Overview of CBP-307

CBP-307 is an S1P1 agonist that is being developed as a treatment for autoimmune diseases by Suzhou Connect Biopharmaceuticals, Ltd. CBP-307 (1-(2-fluoro-4-(5-(4-isobutylphenyl)-1,2,4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid hemihydrate) is a potent, selective, small-molecule agonist of S1P1 and S1P5 receptors. Cell-based assays have confirmed CBP-307 induces internalization of S1P1 from the cell surface. This is consistent with the known mechanism of action of other S1P1 agonists, in that they down-modulate S1P1 and inhibit lymphocyte egress from lymphoid tissues.

1.2.1. Summary of Clinical Experience

The Phase 1 development of CBP-307 comprised 2 completed studies in healthy subjects:

- A single and multiple ascending dose study to evaluate the safety and tolerability of CBP-307 including pharmacokinetic (PK), pharmacodynamic (PD), and food-effect assessments (Study CBP-307AU001)
- A single-dose and multiple-dose, and fixed-dose titration study to evaluate the safety and tolerability of CBP-307 including PK and PD (Study CBP-307CN001)

Currently, CBP-307 is being evaluated in 2 Phase 2 studies:

- Ongoing multicenter study in subjects with moderate to severe ulcerative colitis (Study CBP-307CN002) to compare the clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing

achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

- Ongoing study in subjects with moderate to severe Crohn's disease compares clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

1.2.1.1. Safety

Study CBP-307AU001

A total of 44 healthy subjects were enrolled in the study. There were 28 subjects evaluated using the single-dose regimen (0.1, 0.25, 0.5, and 2.5 mg CBP-307) of which 21 subjects received CBP-307 and 7 subjects received placebo. Another 16 healthy subjects were evaluated using the multiple-dose regimen (0.15 and 0.25 mg CBP-307 given once daily [QD] for 28 consecutive days) of which 12 subjects received CBP-307 and 4 subjects received placebo.

Overall, no unexpected safety signals were identified and no deaths occurred in this study. For the single-dose regiment, no subjects were discontinued due to a treatment-emergent AE (TEAE). In the multiple-dose regimen, there were 2 subjects who were discontinued from the study (due to increased alanine transaminase and second degree AV block [not considered to be clinically significant, as judged by the investigator]). All TEAEs resolved by the end of the study.

In the single-dose regimen groups, TEAEs were reported in 12 of 21 subjects (57.1%) treated with CBP-307 and in 3 of 7 subjects (42.8%) treated with placebo. Most (91.7%) of the TEAEs in these subjects were mild in severity. The most common TEAEs in the CBP-307-treated groups were headache (28.6%); dizziness (19.0%); and bradycardia (9.5%). Bradycardia was reported only in 2 subjects receiving the highest (2.5 mg) CBP-307 dose. One subject had a serious adverse event (SAE) of bradycardia (associated with transient asystole) following a single dose of 2.5 mg CBP-307.

In the multiple-dose regimen groups, CBP-307 at doses of 0.15 and 0.25 mg QD was generally well tolerated over the 28 days of dosing. Treatment-emergent AEs were reported in 11 of 12 subjects (91.7%) in the CBP-307 groups and 2 of 4 subjects (50.0%) in the placebo groups. Most (83.3%) TEAEs were mild in severity. The most common TEAEs in the 2 CBP-307 groups were headache (50.0%), and fatigue, nausea, and musculoskeletal pain (16.7% each). The incidences of these TEAEs were similar in both CBP-307-treated groups. No SAEs were reported for subjects in the multiple-dose regimen.

Study CBP-307CN001

A total of 30 eligible subjects completed 3 CBP-307 dose groups in ascending order of dose after randomization (in a ratio of 1:1:1): Group A (0.1 mg), Group B (0.2 mg), and Group C (0.3 mg). Each dose group consisted of 10 subjects, including 8 subjects receiving the investigational drug and 2 subjects receiving placebo by random assignment. The administration started from the dose of 0.1 mg. The subjects in this group received a single

dose of CBP-307 or placebo and were followed up for safety and tolerance within the next 7 days. Then the subjects received 0.1 mg CBP-307 or placebo QD for 14 consecutive days and were followed up for safety and tolerance within the next 7 days. Dose escalation did not occur until the review of the single-dose regimen safety data from the 6 subjects in the previous dose cohort, and the safety data did not meet the termination criteria. The subjects in the dose of 0.3 mg received fixed-dose titration regimen, ie, 0.05 mg CBP-307 or placebo QD for 3 consecutive days; 0.1 mg CBP-307 or placebo QD for 2 consecutive days; 0.2 mg CBP-307 or placebo QD for 2 consecutive days; finally, 0.3 mg CBP-307 or placebo QD for 14 consecutive days, and the subjects were followed up for safety and tolerance within the next 7 days.

Overall, no unexpected safety signals were identified, and there were no deaths, SAEs, or AEs leading to the subject's early withdrawal from the study after administration of CBP-307. In the safety set, a total of 29 subjects (8 in Group A, 100%; 8 in Group B, 100%; 8 in Group C, 100% and 5 in placebo group, 83.3%) experienced TEAEs.

During the single-dose period, a total of 14 subjects (5 of 8 in Group A, 62.5%; 6 of 8 in Group B, 75%, and 3 of 4 in placebo group, 75%) developed AEs. The incidence of TEAEs in Group A was generally similar to the placebo group. Among TEAEs in Group B, the incidence of AEs related to abnormalities in investigations was higher than that in placebo group, including lymphocyte count decreased (12.5%), white blood cell (WBC) count decreased (12.5%), neutrophil count decreased (12.5%), alanine aminotransferase increased (25%), and gamma-glutamyltransferase increased (12.5%), and aspartate aminotransferase increased (12.5%). Additionally, 1 subject experienced heart rate (HR) decreased (12.5%).

During dose-titration period, 2 subjects (2 of 8 in Group C, 25%) experienced TEAEs. The TEAEs reported in Group C during the titration period included cough (12.5%) and increased upper airway secretion (12.5%). There were no TEAEs in the placebo group during this period.

During repeated-dose period, a total of 28 subjects (8 of 8 in Group A, 100%; 8 of 8 in Group B, 100%; 8 of 8 in Group C, 100%; and 4 of 6 in placebo group, 66.7%) experienced AEs. The most frequent TEAE in Group A was upper respiratory tract infection (37.5%) compared with placebo group; the most frequent TEAEs in Group B and Group C included decreased lymphocyte count (Group B, 87.5%; Group C, 100.0%), WBC count (Group B, 87.5%; Group C, 62.5%), and neutrophil count (Group B, 50%; Group C, 12.5%). The TEAEs noted in Group B during the repeated-dose period also included increased alanine aminotransferase (25%), gamma-glutamyltransferase (37.5%), and aspartate aminotransferase (12.5%), upper respiratory tract infection (12.5%), influenza (12.5%), chest pain (12.5%), lethargy (25%), and neck pain (12.5%); TEAEs in Group C during the repeated-dose period also included increased alanine aminotransferase (25%), decreased HR (12.5%), and mouth ulcer (12.5%); the TEAEs in placebo group included increased transaminase (16.7%), prolonged activated partial thromboplastin time (1/6, 16.7%), decreased hemoglobin (16.7%), upper respiratory tract infection (16.7%), diarrhea (16.7%), dizziness (16.7%), and palpitations (16.7%).

Study CBP-307CN002

This study is ongoing and there are no safety data available.

Study CBP-307CN003

This study is ongoing and there are no safety data available.

1.2.1.2. Pharmacokinetics

CBP-307 given orally as a single dose was readily absorbed; drug concentrations peaked at approximately 6 hours after administration, with an elimination apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours (range of 23 to 29 hours). The time to maximum observed concentration (C_{max}) in the blood was delayed from 6 hours to approximately 10 hours when CBP-307 was given with a high-fat diet. Food consumption also increased exposure (Table 1).

For the single-dose administration, CBP-307 exposure (based on C_{max} and area under the concentration-time curve [AUCs]) increased with increasing dose following a single-dose administration (Table 1).

Table 1: Pharmacokinetics Parameters in the Single-Dose CBP-307 Regimen (Study CBP-307AU001)

Single-Dose Regimen PK Parameters	Mean CBP-307 Single Dose ± SEM (n)				
	0.1 mg	**0.25 mg**	**0.5 mg (fasted)**	**0.5 mg (fed)[a]**	**2.5 mg**
AUC_{last} (ng*h/mL)	13.4 ± 3.54 (n = 6)	45.1 ± 5.25 (n = 6)	160 ± 22.8 (n = 6)	290 ± 28.1 (n = 6)	550 ± 96.3 (n = 3)
AUC_{inf} (ng*h/mL)	ND	63.7 ± 2.14 (n = 3)	214 ± 58.3 (n = 3)	355 ± 44.3 (n = 5)	710 ± 164 (n = 2)
C_{max} (ng/mL)	0.537 ± 0.0931 (n = 6)	1.53 ± 0.0935 (n = 6)	4.84 ± 0.706 (n = 6)	8.58 ± 1.11 (n = 6)	19.0 ± 3.55 (n = 3)
t_{max} (hours)	7.33 ± 1.33 (n = 6)	5.33 ± 0.99 (n = 6)	5.00 ± 0.86 (n = 6)	10.67 ± 2.72 (n = 6)	6.00 ± 2.00 (n = 3)
$t_{1/2}$ (hours)	ND	23.3 ± 1.70 (n = 3)	28.8 ± 1.28 (n = 3)	26.0 ± 1.17 (n = 5)	22.8 ± 3.96 (n = 2)

Abbreviations: AUC_{inf} = area under the curve at infinity; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; h = hour(s); mg = milligram(s); ND = not determinable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SEM = standard error of the mean; $T_{1/2}$ = elimination half-life; T_{max} = time to maximum concentration.
[a] Study Part 1b: Cohort 3 from Part 1a returned to receive a single oral dose of CBP-307 at 0.5 mg under fed conditions.
Source: Final report for Study CBP-307AU001.

For the repeated-dose administration of CBP-307, the C_{max} and AUCs increased with the higher administered dose (Table 2). At the steady-state timepoint on Day 28, the median CBP-307 t_{max} was 4 to 6 hours. The average $t_{1/2}$ was similar, ranging 44 to 49 hours, and there were no dose-dependent changes in $t_{1/2}$ within the dose range. The $t_{1/2}$ was slightly prolonged after repeated-dose administration when compared with that after a single-dose administration. Moderate accumulation of CBP-307 (approximately 3 times the levels

following a single dose) was noted in plasma after QD administration for 14 consecutive days.

Table 2: Pharmacokinetics Parameters in the Multiple-Dose CBP-307 Regimen (Study CBP-307AU001)

Multiple-Dose Regimen PK Parameters	Multiple-Dose Cohort 1 CBP-307 Dosing, mg (± SD) (n)		Multiple-Dose Cohort 2 CBP-307 Dosing, mg (± SD) (n)	
	Day 1 0.1	Day 28 0.25	Day 1 0.15	Day 28 0.15
AUC_{0-24} (ng*h/mL)	24.5 ± 3.26 (n = 5)	125 ± 12.4 (n = 4)	26.3 ± 7.45 (n = 5)	79.7 ± 27.3 (n = 6)
AUC_{last} (ng*h/mL)	NA	203 ± 21.9 (n = 4)	NA	131 ± 44.7 (n = 6)
C_{max} (ng/mL)	1.45 ± 0.214 (n = 5)	6.30 ± 0.588 (n = 4)	1.32 ± 0.422 (n = 6)	4.23 ± 1.45 (n = 6)
t_{max} (hours)	6.80 ± 1.50 (n = 5)	6.50 ± 1.50 (n = 4)	5.00 ± 0.68 (n = 6)	4.33 ± 0.33 (n = 6)

Abbreviations: AUC_{0-24} = area under the curve from time 0 to 24 hours; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; mg = milligram(s); NA = not applicable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SD = standard deviation; T_{max} = time to maximum concentration.
Source: Final report for Study CBP-307AU001.

1.3. Overview of Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of International Council for/Conference on Harmonisation (ICH) E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[2]

1.4. Study Rationale

Regulatory guidance (ICH E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase 1, 2, and 3 trials may be conducted they usually have an insufficient sample size, infrequent sampling of ECG data, or the use of inadequate controls to overcome the high rate of spontaneous change in QTc duration. This has resulted in regulatory guidance recommending a dedicated or thorough trial to define the ECG effects of new drugs.

This study will be done in healthy subjects to eliminate variables known to have an effect on ECG parameters (concomitant drugs, diseases, etc.). A supratherapeutic dose of CBP-307 is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (eg, concomitant use of cytochrome P450 [CYP]3A4

inhibitor, concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to allow for PK to QTc modeling to assess the effect of drug concentration on cardiac repolarization.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with CBP-307 may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the PK of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on HR, PR and QRS intervals, and T-wave morphology.

2.2. Endpoints

2.2.1. Electrocardiogram Endpoints

2.2.1.1. Primary

The primary endpoint is the change-from-baseline QTcF (ΔQTcF).

2.2.1.2. Secondary

The secondary endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);

- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

2.2.2. Pharmacokinetic Endpoints

Pharmacokinetic parameters of CBP-307 will be determined if data allows:

- area under the concentration‑time curve from time zero extrapolated to infinity (AUC_{inf})
- area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})

Other PK parameters may also be reported.

2.2.3. Safety Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether

volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2, 3 to 6, 7 to 15, and on Day 16 (placebo will be administered to all subjects on Day -1).

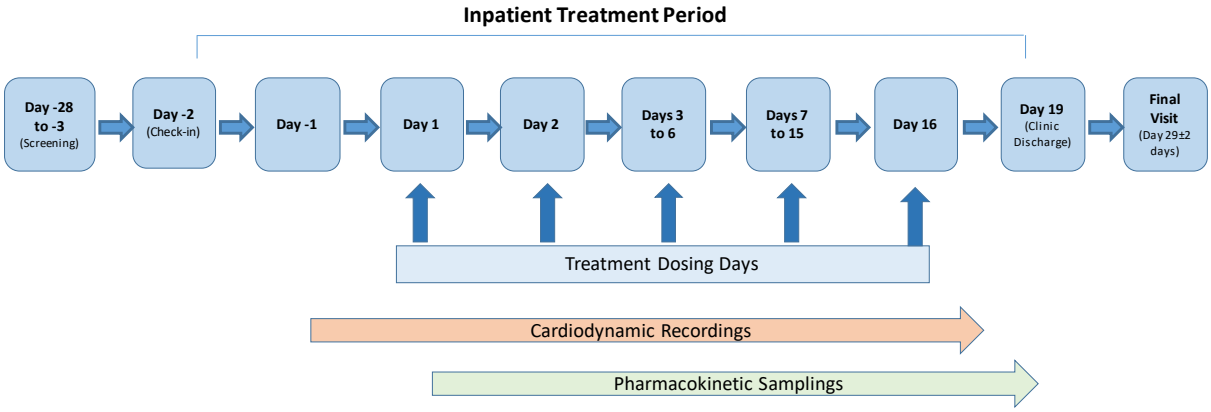
The following treatments will be administered:

- Starting doses of CBP-307 for titration (0.05 mg on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2)
- A therapeutic dose of CBP-307 (0.2 mg, Days 3 to 6)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 7 to 15)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Day 2, Days 3 to 6, Days 7 to 15, and Day 16. Dosing details are provided in Table 3. Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. An end-of-study visit will occur on Day 29±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 19. Treatment administration will occur on Days 1, 2, 3 to 6, 7 to 15, and 16 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 6, 15, and 16 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15. Subjects will return to the study site for a follow-up visit on Day 29±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 6, 15, and 16. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15 (sample collection window: ±30 minutes). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 15, and 16.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit. In addition, subjects will be monitored via cardiac telemetry at specific timepoints during the treatment period.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 59 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for CBP-307 to cause QT prolongation. As CBP-307 exposure affects heart rate, the primary endpoint for this study will be the QTcF.

The study will be randomized and double-blind because randomization eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions, thus eliminating the possibility that the observed effects of the intervention are because of differential use of other treatments.

The sample size for this study is based on a formal statistical power calculation.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Both male and female subjects will be included to eliminate similar known ECG variability effects.

Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Pharmacokinetic assessments of CBP-307 concentrations in plasma will be evaluated during the study. The timepoints for the PK sample collections are based on previous studies and are considered adequate to allow for the characterization of the drug's PK after oral dosing. Furthermore, the chosen PK sample collection for CBP-307 is anticipated to be sufficient to allow reasonable estimation of $t_{1/2}$ during the terminal elimination phase.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.05 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.1 mg on Day 2 and a dose of 0.2 mg on Days 3 to 6. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index between 18.0 and 30.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and confirmed at check-in as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4. Negative pregnancy test for females of childbearing potential at screening (blood test) and check-in (urine test);
5. Supine diastolic blood pressure between 60 and 90 mmHg and systolic blood pressure between 90 and 140 mmHg (inclusive) at screening on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest;
6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and ≤470 msec for females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.
7. Has serum potassium, calcium, and magnesium levels within the normal reference range at screening, as judged by the investigator.
8. Able to swallow multiple tablets (based on subject's verbal confirmation).
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Subject is mentally or legally incapacitated or has had significant history of recent mental health issues requiring medication and/or hospitalization at the time of the screening visit or expected during the conduct of the study.

2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee). *Note: Childhood asthma that is considered recovered or seasonal allergies that are not currently active or requiring treatment are allowed.*
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
4. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
5. History of significant multiple and/or severe allergies (eg, latex allergy, band-aids, adhesive dressing, or medical tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.
6. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs within 6 months prior to the first dose of study drug (uncomplicated appendectomy and hernia repair will be allowed).
7. History or presence of:
    a. Hypokalemia, in the opinion of the investigator (or designee);
    b. Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
    c. Sick sinus syndrome, second, or third degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities;
    d. Repeated or frequent syncope or vasovagal episodes;
    e. Hypertension, angina, bradycardia, or severe peripheral arterial circulatory disorders.
8. Clinically significant abnormalities (as judged by the investigator in laboratory tests results [out-of-range results confirmed on repeat]), including but not limited to the following parameters:
    a. alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin greater than 1.5 × upper limit of normal;
    b. hemoglobin <10 g/dL, WBC <3.0 $\times 10^9$/L, neutrophils <1.5 $\times 10^9$/L, lymphocytes <0.8 $\times 10^9$/L and platelets <100 $\times 10^9$/L or >1200 $\times$ 10^9/L;
9. History or evidence of alcoholism or drug/chemical abuse within 2 years prior to check-in.
10. Alcohol consumption of >10 units per week for males and females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
11. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.

12. Positive hepatitis panel, positive syphilis test, and/or positive human immunodeficiency virus test (Appendix 2).
13. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 28 days prior to the first dose of study treatment on Day 1. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
14. Participation in a previous clinical study where subjects received CBP-307.
15. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 28 days prior to first dose of study treatment on Day 1.
16. Use or intend to use any prescription medications/products within 14 days prior to first dose of study drug (Day 1) and throughout the study, unless deemed acceptable by the investigator (or designee). *Note: For females only, the use hormonal contraception, hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives within 14 days prior to Day 1 is not acceptable, except for Mirena®.*
17. Use or intend to use any drugs known to be significant inhibitors or inducers of CYP enzymes and/or P-gp, including St. John's Wort, for days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the investigator or designee to confirm the lack of PK/PD interaction with the study drug.
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intend to use any nonprescription medications/products including antacids, vitamins (especially those containing magnesium, aluminum, iron, or zinc), minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
21. Has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for whatever reason), in the opinion of the investigator, within the 28 days prior to the first dose of study treatment, and throughout the study.
22. Consumption of caffeine/xanthine-containing foods or beverages within 48 hours prior to check-in until discharge.
23. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
24. Receipt of blood products within 2 months prior to check-in.
25. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
26. Poor peripheral venous access.

27. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Eligible subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). The screening number will be used on all safety samples throughout the study. Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw their informed consent from the study at any time or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, or the inability of the subject to comply with the protocol-required visits or procedures. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- investigator decides to terminate the study due to safety concerns such as AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development
- sponsor requests for termination (eg, due to financial or management reasons, etc.) under the premise to fully protect the safety and rights of subjects
- health authority or ethics committee (EC) orders the termination of the trial for any reason.

Definition of end-of-treatment and end-of-study

- end-of-treatment is completion of safety follow-up or withdrawal from the study. End-of-study is the last visit by the last subject.

5. STUDY TREATMENTS

Study treatments are defined as any investigational product (IP), non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as IMP and non-IMP, respectively.

5.1. Investigational Products

The details regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 will be provided in a separate document. Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Table 3: Study Treatments

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Form		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.05 mg 0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.05 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Day 2	Group 1	1 × 0.1 mg			
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Days 3 to 6	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 7 to 15	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 16	Group 1				1 tablet
	Group 2A				1 tablet
	Group 2B			1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosing Instructions		Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	Treatments will be administered after the completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

All supplies of the IMP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study treatments will be stored at the study site in a location that is locked with restricted access.

5.2. Study Treatment Administration

Each dose of study treatment (CBP-307, placebo, or moxifloxacin) will be administered orally following an overnight fast of at least 10 hours, with approximately 240 mL of room temperature water. Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Subjects will be dosed in numerical order while sitting or standing but not be permitted to lie supine for 2 hours after treatment administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a double-blind randomized study. Subjects will be randomized to one of the treatment sequences before administration of the first dose of study treatment. A randomization list will be generated by a statistician using a computer-generated pseudo-random permutation procedure. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the study site. Randomization details will be included in the randomization specification.

5.4. Blinding

This is a double-blinded study. The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to CBP-307 or moxifloxacin.
- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.
- Interim bioanalytical data will be provided to Covance Early Clinical Biometrics in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing coded details of the treatment. These individually sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until the completion of the study.

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site's pharmacy (RAH Pharmacy), per the sponsor's written instructions. If destruction is authorized to take place at the study site's pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from the use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the investigator (or designee) and/or sponsor have given their prior consent. Medications taken within 28 days before study treatment administration will be documented as a prior treatment. Treatments taken after study treatment administration will be documented as concomitant treatments.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for the treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Females will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives (with the exception of Mirena®) during the study until the follow-up visit (See Appendix 4).

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 29±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 19.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 19 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 29±2 days.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until the follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 29±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

This study includes a screening period (Day -28 to Day -3), a treatment period (Days -2 to 19), and a follow-up period (Day 29 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

7.1. General Assessments

7.1.1. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.1.2. Medical History

At the timepoint specified in Appendix 6, the investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

Continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. All ECG data will be collected using a Holter (or Mortara Surveyor) ECG continuous 12-lead digital recorder. The 12-lead Holter (or Mortara Surveyor) ECG equipment will be supplied and supported by ERT (eResearch Technology Inc., Philadelphia, PA). The continuous 12-lead digital ECG data will be stored onto SD memory cards.

The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT (eResearch Technology Inc., Philadelphia, PA). The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints and subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter (or Mortara Surveyor) recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically,

the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position).

7.2.1.2. Expert Precision QT Analysis

Expert precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc, or RR from beat-to-beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR values from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS interval of the ECG (QRS) intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed (ie, changes not present at baseline). For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline.

7.2.2. Safety 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria applies:

- QT interval corrected for HR using Fridericia's method (QTcF) is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.3. Cardiac Telemetry Monitoring

Subjects will be monitored via cardiac telemetry from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days; as described in Appendix 6). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary.

The start and stop date and time of the telemetry monitoring will be recorded in the eCRFs. Clinically significant abnormalities noted from telemetry monitoring will be confirmed by 12-lead ECG if necessary, then after confirming, the abnormities will be reported as AEs in the eCRF.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 × 3 mL for CBP-307 and moxifloxacin assays) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of CBP-307 and moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the follow-up visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of placebo administration to all subjects (Day -1) until study completion. If AEs that occur in the screening prior to placebo administration to all subjects (Day -1) are considered to be related to the study procedure, they should be also collected. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator’s (or designee’s) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

A serum qualitative pregnancy or urine test (females only) and follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test. All pregnancies should be reported as specified in Appendix 1.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. At the discretion of the investigator, clinically significant clinical laboratory assessments may be confirmed by repeat sampling. If the clinical significance is confirmed, subjects will be excluded from participation or, if already included, will be followed until normalization of the test result or for as long as the investigator considers necessary.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.4.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and tympanic temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Physical examinations include general appearance, head, eyes,

ears, nose, and throat, neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, skin, and others.

Height, weight, and body mass index will be assessed at screening.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Sample Size for Primary Analysis:

A sample size of 28 evaluable subjects per treatment group will provide more than 94.4% power to exclude that CBP-307 causes more than 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QT effect (ΔΔQTcF) at the observed geometric mean C_{max} of CBP-307 in the study. This power is estimated approximately using a 2-sample t-test. The calculation assumes a 1-sided 5% significance level, an underlying effect of CBP-307 of 3 msec and a standard deviation (SD) of the ΔQTcF of 8 msec for both CBP-307 and placebo treatment groups. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed-effects model. The concentration-QTc analysis method is supported by Darpo et al 2015[3] and Ferber et al, 2015,[4] and consistent with the experiences from 25 recent TQT studies.

Sample Size Considerations for Assay Sensitivity:
To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.64 required to guarantee a power of at least 95% in a paired t-test situation with a sample size of 28 evaluable subjects. In other words, based on this calculation, a power of at least 95% will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD from the by-timepoint analysis, does not exceed 6.9 msec (ie, 128% [= 0.82/0.64] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects.[5]

8.2. Analysis Populations

8.2.1. Cardiodynamic Population

The QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value. The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

The PK/QTc population will include all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for CBP-307, and for moxifloxacin.

The as-treated principle will be applied to all analysis populations mentioned below.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of investigational product and have evaluable PK data of any of the analytes (CBP-307 and moxifloxacin). A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of investigational product drug (therapeutic and supratherapeutic doses of CBP-307, moxifloxacin, or placebo).

8.3. Cardiodynamic ECG Analyses

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP-307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 16, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 15 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 16, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 15.

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 6, and 15 categorical) as fixed effects, and a random intercept and slope per subject.[6]

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 6, and 15, and Days 1 and 16 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 6 and 15 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF (ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 6 and 15 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max}

<10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 6 and 15; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 6 and 15; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 6 and 15, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 6, and 15: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 15, and corresponding placebo), and

time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 6, and 15 at each postbaseline timepoint on Days 1, 6, and Day 15, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 16. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 16: categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

8.4. Pharmacokinetic Analyses

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, SD, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by group. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_Z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)
- Accumulation ratio (R_{ac}) for C_{max} ($R_{ac[Cmax]}$) and $R_{ac(AUC0-24)}$, calculated as Day 15 C_{max}/Day 7 C_{max} and Day 15 AUC_{0-24}/Day 7 AUC_{0-24}, respectively.

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Other parameters may be added as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the Statistical Analysis Plan.

8.5. Safety Analysis

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

8.6. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication.

Examples of AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving clinically significant abnormal laboratory tests, ECG, etc.)
- Exacerbation of previous condition, including increased incidence and/or severity.

Note: Regarding decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. All AEs will be recorded in the medical records and eCRFs. The investigator (or designee) is to record in detail any AE that occurred to the subject, including: AE diagnosis whenever possible, or signs, symptoms, the start date and time of occurrence, the stop date and time of occurrence, seriousness (ie, whether it is an SAE), severity of AEs, causality assessment, actions taken on the investigational product, other actions (eg, medications/treatments given), and outcomes of AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: 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, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

All SAEs will be collected after subjects sign the informed consent form and throughout the entire study, ie, until the end-of-study as specified in the protocol (or at early termination).

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor (or designee).

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The investigator will complete an SAE report form and forward it by facsimile or email to Covance APAC Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to: +61-2-8879-2000

SAE Reporting email: SAEIntake@covance.com (preferred method)

Covance Safety SAE Reporting Fax Number: 61-2-6100-9788 or 1800-882-203 (toll free)

The responsibilities of Covance APAC Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Covance APAC Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the EC, Medicines and Healthcare Products Regulatory Agency, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

For SAEs, the active reporting period to sponsor or its designated representative begins from the time that the subject provides informed consent through to the last subject visit.

Nonserious AEs should be collected from the time the subject has taken the placebo dose on Day -1 through the last subject visit. If AEs that occur in the screening prior to the placebo administration to all subjects on Day -1 are considered to be related to the study procedure, they should be also collected.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, the sponsor should be notified within 24 hours of investigator awareness of the event. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting as specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

If the female subject becomes pregnant during the clinical trial and has not yet been dosed with study treatment, she must be withdrawn from the study. If the female subject becomes pregnant during the clinical trial and has been dosed, she must discontinue treatment immediately but may remain on study for safety evaluations. If the partner of a male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should report to the sponsor or designee in a pregnancy report form within 24 hours after investigator awareness and report to the EC in time as per local requirement.

The investigator will follow up on pregnancy outcomes, until not less than 12 months after birth, unless otherwise justified, and will report the outcome to the sponsor and ethics committee.

If any adverse pregnancy outcome (eg, the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformations), it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if indicated by dipstick)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen Syphilis	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol Tricyclic antidepressants Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b] **Other Tests** Low density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	41	328
Total:			390.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the follow-up visit. Primary (non-barrier) methods of contraception include:

- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation or bilateral salpingectomy
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- non-hormonal intrauterine device or Mirena® (other hormonal intrauterine devices will not be allowed) in place for at least 3 months prior to the first dose of the study drug
- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom without spermicide
- female condom without spermicide
- cervical cap without spermicide (as prescribed)
- diaphragm without spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom without spermicide) in addition to a second method of acceptable contraception from check-in until 90 days after the follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- cervical cap without spermicide
- diaphragm without spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a

subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol, local legal and regulatory requirements and with the following:

- General principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the human research ethics committee (HREC) by the investigator and reviewed and approved by the HREC before the study is initiated.

Any protocol amendments will require EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the HREC. All correspondence with HREC should be retained in the investigator file. A copy of HREC approval should be forwarded to the sponsor.

- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of SAEs or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the EC, and all other applicable local regulations.

Regulatory Authority

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following the discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed as follows:The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all

manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Informed consent	X													
Eligibility criteria review (Inclusion/Exclusion)	X	X												
Demographics	X													
Medical history	X													
Admission to clinical research unit[1]		X												
Discharge from clinical research unit[2]													X	
Randomization				X										
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X													
Physical exam	X	X												X
Hematology	X	X					X						X	X
Clinical chemistry (including cholesterol panel tests)	X	X					X						X	X
Urinalysis	X	X											X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X													
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X			X	X
Cardiac Telemetry Monitoring[9]				X	X	X (Day 3)		X (Day 7)						

Schedule of Assessments

Study Period	Screening	In-house Treatment Period												End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 14**	**15**	**16**	**17**	**18**	**19**	**29±2**
Breath alcohol, urine drug toxicology and cotinine	X	X												
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X			X		X	X				
Pregnancy test[6]	X	X												X
Follicle -stimulating hormone test (postmenopausal females only)	X													
CBP-307/placebo administration			X	X	X	X	X	X	X					
Moxifloxacin/placebo administration				X						X				
Blood sampling for PK[7,8]				X			X		X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 96-hour PK samples and after completion of safety assessments on Day 19.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Days 17, 18, and 19):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Days 17 and 18:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure at approximately the same time each day. **Discharge (Day 19):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 29±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.

4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days (except for Days 17 and 18) and before discharge on Day 19. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 6, 15, and 16. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. When timepoints for ECG extraction, safety ECGs, vital signs assessment, and blood draws coincide, procedures will be performed in this order. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 6 (therapeutic concentrations versus placebo), and Day 15 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 15, and 16.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 29±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 6, 15, and 16). Additional PK samples will be collected at 72 and 96 hours following dosing on Day 15.
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24, 72, and 96 hours postdose.
9. Subjects will be monitored via cardiac telemetry during the treatment period from approximately 1 hour prior to dose administration and until approximately 12 hours postdose on Days 1, 2, 3, and 7 (up-titration days). Based on the emerging safety data from the study, the duration of the telemetry may be extended if necessary. The start and stop date and time of the telemetry monitoring will be recorded in the eCRF.

Protocol

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Protocol Status: Final
Protocol Date: 18 March 2021
Protocol Version: 1.0

Investigational Medicinal Product: CBP-307

Protocol Reference Number: CBP-307AU002
Covance Study Number: 8463245
IND Number: 134585

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Sponsor Signatory:
Ping Li, MD

Principal Investigator:
Nicholas Farinola, MBBS

SPONSOR APPROVAL

I have read the protocol and approve it:

DocuSigned by:
Ping Li
4C556BD506CD4EA...

3/19/2021

Ping Li, MD
VP, Clinical Development Asia

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

Nicholas Farinola, MBBS
Principal Investigator

23 MAR 2021.
Date

STUDY IDENTIFICATION

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SYNOPSIS

Study Title

A Phase I, Single-center, Randomized, Double-blind, Double-dummy, Placebo- and Positive-Controlled Study to Investigate the Effects of CBP-307 on the QT_C Interval in Healthy Subjects

Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the pharmacokinetics (PK) of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on heart rate (HR), PR and QRS intervals, and T-wave morphology.

Study Design

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only serious adverse events (SAEs) will be reported. After placebo administration to all subjects on Day -1, all adverse events (AEs), whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on

Days 1, 2 to 5, 6 to 14, and on Day 15 (placebo will be administered to all subjects on Day -1).

The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1)
- A therapeutic dose of CBP-307 (0.2 mg, Day 2 to 5)
- A supratherapeutic dose of CBP-307 (0.5 mg, Day 6 to 14)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 16. Treatment administration will occur on Days 1, 2 to 5, 6 to 14, and 15 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic electrocardiogram (ECG) monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 5, 14, and 15 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Subjects will return to the study site for a follow-up visit on Day 28±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 5, 14, and 15. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14

(supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 14, and 15.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 58 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

Number of Subjects

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1; oral capsule)
- A therapeutic dose of CBP-307 (0.2 mg, Day 2 to 5; oral capsule)
- A supratherapeutic dose of CBP-307 (0.5 mg, Day 6 to 14; oral capsule)
- Placebo (matched to moxifloxacin, oral tablet and CBP-307; oral capsule)
- Moxifloxacin (400 mg; oral tablet).

Duration of Subject Participation in the Study

Duration of subject participation from the screening visit through follow-up visit will be up to approximately 26 days for screening period (Days -28 to -3), 18 days for the in-house

treatment period (Days -2 to 16), and 12 ±2 days for follow-up (Day 28±2 days), in total approximately 58 days.

Endpoints

Electrocardiogram (Cardiodynamic):

The primary cardiodynamic endpoint is the change-from-baseline QTcF (ΔQTcF).

The secondary cardiodynamic endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);
- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CBP-307. The PK parameters of CBP-307 will be calculated using a model independent approach. The following PK parameter endpoints will be calculated: maximum observed concentration (C_{max}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}), and time of the maximum observed concentration (t_{max}). Other noncompartmental parameters may be reported.

Safety:

Adverse events, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12-lead ECGs, and vital signs measurements.

Statistical Methods

Cardiodynamic evaluation:

The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of CBP-307 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma levels. Placebo-corrected ΔHR, ΔPR, ΔQRS, and ΔQTcF (ΔΔHR, ΔΔPR, ΔΔQRS, and ΔΔQTcF) will also be evaluated at each postdosing timepoint ('by-timepoint' analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.

Pharmacokinetics:

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by cohort. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

Pharmacokinetic/electrocardiography analyses:

The relationship between CBP-307 plasma concentrations and the change from ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

Safety:

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CRO	contract research organization
CYP	cytochrome P450
Δ	change-from-baseline
ΔΔ	placebo-corrected or placebo-adjusted change-from-baseline
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HR	heart rate
HREC	human resource ethics committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IP	investigational product
LOESS	locally estimated scatterplot smoothing
LS	least squares
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
QD	once daily
QTc	heart-corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SD	standard deviation

SE	standard error
S1P1	sphingosine-1-phosphate receptor 1
TEAE	treatment-emergent adverse event(s)
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
TQT	thorough QT
V_z/F	apparent volume of distribution
WBC	white blood cell
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

Refer to the investigator's brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Disease Background

Autoimmune diseases are serious disorders that afflict a large portion of the world population; most have no cures. Significant advances have been made in the development of novel and disease-modifying therapies, but many of these new treatments have significant side effects. Treatments are needed that provide better risk-to-benefit profiles than the existing therapeutic choices.

T cells are important immune cells that mediate the development of autoimmune disorders. Migration of T cells from lymphoid tissues to the sites of inflammation is central to the functions of T cells, and this process is dependent on sphingosine-1-phosphate (S1P) receptor 1 (S1P1) which is known to ameliorate a variety of autoimmune diseases in animals and humans. Down modulation of this receptor, using S1P1 agonists, prevents T cell egress and results in a reduced number of circulating lymphocytes, particularly the CD4+- and CD8+-naïve and central-memory T cell subsets.

1.2. Overview of CBP-307

CBP-307 is an S1P1 agonist that is being developed as a treatment for autoimmune diseases by Suzhou Connect Biopharmaceuticals, Ltd. CBP-307 (1-(2-fluoro-4-(5-(4-isobutylphenyl)-1,2,4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid hemihydrate) is a potent, selective, small-molecule agonist of S1P1 and S1P receptor 5. Cell-based assays have confirmed CBP-307 induces internalization of S1P1 from the cell surface. This is consistent with the known mechanism of action of other S1P1 agonists, in that they down-modulate S1P1 and inhibit lymphocyte egress from lymphoid tissues.

1.2.1. Summary of Clinical Experience

The Phase 1 development of CBP-307 comprised 2 completed studies in healthy subjects:

- A single and multiple ascending dose study to evaluate the safety and tolerability of CBP-307 including pharmacokinetic (PK), pharmacodynamic (PD), and food-effect assessments (Study CBP-307AU001)
- A single-dose and multiple-dose, and fixed-dose titration study to evaluate the safety and tolerability of CBP-307 including PK and PD (Study CBP-307CN001)

Currently, CBP-307 is being evaluated in 2 Phase 2 studies:

- Ongoing multicenter study in subjects with moderate to severe ulcerative colitis (Study CBP-307CN002) to compare the clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing

achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

- Ongoing study in subjects with moderate to severe Crohn's disease compares clinical efficacy by evaluating the clinical response to CBP-307 versus placebo and the clinical remission and mucosal healing achieved by CBP-307 versus placebo and to compare the clinical safety and tolerability of CBP-307 with those of placebo.

1.2.1.1. Safety

Study CBP-307AU001

A total of 44 healthy subjects were enrolled in the study. There were 28 subjects evaluated using the single-dose regimen (0.1, 0.25, 0.5, and 2.5 mg CBP-307) of which 21 subjects received CBP-307 and 7 subjects received placebo. Another 16 healthy subjects were evaluated using the multiple-dose regimen (0.15 and 0.25 mg CBP-307 given once daily [QD] for 28 consecutive days) of which 12 subjects received CBP-307 and 4 subjects received placebo.

Overall, no unexpected safety signals were identified and no deaths occurred in this study. For the single-dose regiment, no subjects were discontinued due to a treatment-emergent AE (TEAE). In the multiple-dose regimen, there were 2 subjects who were discontinued from the study (due to increased alanine transaminase and second degree AV block [not considered to be clinically significant, as judged by the investigator]). All TEAEs resolved by the end of the study.

In the single-dose regimen groups, TEAEs were reported in 12 of 21 subjects (57.1%) treated with CBP-307 and in 3 of 7 subjects (42.8%) treated with placebo. Most (91.7%) of the TEAEs in these subjects were mild in severity. The most common TEAEs in the CBP-307-treated groups were headache (28.6%); dizziness (19.0%); and bradycardia (9.5%). Bradycardia was reported only in 2 subjects receiving the highest (2.5 mg) CBP-307 dose. One subject had a serious adverse event (SAE) of bradycardia (associated with transient asystole) following a single dose of 2.5 mg CBP-307.

In the multiple-dose regimen groups, CBP-307 at doses of 0.15 and 0.25 mg QD was generally well tolerated over the 28 days of dosing. Treatment-emergent AEs were reported in 11 of 12 subjects (91.7%) in the CBP-307 groups and 2 of 4 subjects (50.0%) in the placebo groups. Most (83.3%) TEAEs were mild in severity. The most common TEAEs in the 2 CBP-307 groups were headache (50.0%), and fatigue, nausea, and musculoskeletal pain (16.7% each). The incidences of these TEAEs were similar in both CBP-307-treated groups. No SAEs were reported for subjects in the multiple-dose regimen.

Study CBP-307CN001

A total of 30 eligible subjects completed 3 CBP-307 dose groups in ascending order of dose after randomization (in a ratio of 1:1:1): Group A (0.1 mg), Group B (0.2 mg), and Group C (0.3 mg). Each dose group consisted of 10 subjects, including 8 subjects receiving the investigational drug and 2 subjects receiving placebo by random assignment. The administration started from the dose of 0.1 mg. The subjects in this group received a single

dose of CBP-307 or placebo and were followed up for safety and tolerance within the next 7 days. Then the subjects received 0.1 mg CBP-307 or placebo QD for 14 consecutive days and were followed up for safety and tolerance within the next 7 days. Dose escalation did not occur until the review of the single-dose regimen safety data from the 6 subjects in the previous dose cohort, and the safety data did not meet the termination criteria. The subjects in the dose of 0.3 mg received fixed-dose titration regimen, ie, 0.05 mg CBP-307 or placebo QD for 3 consecutive days; 0.1 mg CBP-307 or placebo QD for 2 consecutive days; 0.2 mg CBP-307 or placebo QD for 2 consecutive days; finally, 0.3 mg CBP-307 or placebo QD for 14 consecutive days, and the subjects were followed up for safety and tolerance within the next 7 days.

Overall, no unexpected safety signals were identified, and there were no deaths, SAEs, or AEs leading to the subject's early withdrawal from the study after administration of CBP-307. In the safety set, a total of 29 subjects (8 in Group A, 100%; 8 in Group B, 100%; 8 in Group C, 100% and 5 in placebo group, 83.3%) experienced TEAEs.

During the single-dose period, a total of 14 subjects (5 of 8 in Group A, 62.5%; 6 of 8 in Group B, 75%, and 3 of 4 in placebo group, 75%) developed AEs. The incidence of TEAEs in Group A was generally similar to the placebo group. Among TEAEs in Group B, the incidence of AEs related to abnormalities in investigations was higher than that in placebo group, including lymphocyte count decreased (12.5%), white blood cell (WBC) count decreased (12.5%), neutrophil count decreased (12.5%), alanine aminotransferase increased (25%), and gamma-glutamyltransferase increased (12.5%), and aspartate aminotransferase increased (12.5%). Additionally, 1 subject experienced heart rate (HR) decreased (12.5%).

During dose-titration period, 2 subjects (2 of 8 in Group C, 25%) experienced TEAEs. The TEAEs reported in Group C during the titration period included cough (12.5%) and increased upper airway secretion (12.5%). There were no TEAEs in the placebo group during this period.

During repeated-dose period, a total of 28 subjects (8 of 8 in Group A, 100%; 8 of 8 in Group B, 100%; 8 of 8 in Group C, 100%; and 4 of 6 in placebo group, 66.7%) experienced AEs. The most frequent TEAE in Group A was upper respiratory tract infection (37.5%) compared with placebo group; the most frequent TEAEs in Group B and Group C included decreased lymphocyte count (Group B, 87.5%; Group C, 100.0%), WBC count (Group B, 87.5%; Group C, 62.5%), and neutrophil count (Group B, 50%; Group C, 12.5%). The TEAEs noted in Group B during the repeated-dose period also included increased alanine aminotransferase (25%), gamma-glutamyltransferase (37.5%), and aspartate aminotransferase (12.5%), upper respiratory tract infection (12.5%), influenza (12.5%), chest pain (12.5%), lethargy (25%), and neck pain (12.5%); TEAEs in Group C during the repeated-dose period also included increased alanine aminotransferase (25%), decreased HR (12.5%), and mouth ulcer (12.5%); the TEAEs in placebo group included increased transaminase (16.7%), prolonged activated partial thromboplastin time (1/6, 16.7%), decreased hemoglobin (16.7%), upper respiratory tract infection (16.7%), diarrhea (16.7%), dizziness (16.7%), and palpitations (16.7%).

Study CBP-307CN002

This study is ongoing and there are no safety data available.

Study CBP-307CN003

This study is ongoing and there are no safety data available.

1.2.1.2. Pharmacokinetics

CBP-307 given orally as a single dose was readily absorbed; drug concentrations peaked at approximately 6 hours after administration, with an elimination apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours (range of 23 to 29 hours). The time to maximum observed concentration (C_{max}) in the blood was delayed from 6 hours to approximately 10 hours when CBP-307 was given with a high-fat diet. Food consumption also increased exposure (Table 1).

For the single-dose administration, CBP-307 exposure (based on C_{max} and area under the concentration-time curve [AUCs]) increased with increasing dose following a single-dose administration (Table 1).

Table 1: Pharmacokinetics Parameters in the Single-Dose CBP-307 Regimen (Study CBP-307AU001)

Single-Dose Regimen PK Parameters	Mean CBP-307 Single Dose ± SEM (n)				
	0.1 mg	**0.25 mg**	**0.5 mg (fasted)**	**0.5 mg (fed)[a]**	**2.5 mg**
AUC_{last} (ng*h/mL)	13.4 ± 3.54 (n = 6)	45.1 ± 5.25 (n = 6)	160 ± 22.8 (n = 6)	290 ± 28.1 (n = 6)	550 ± 96.3 (n = 3)
AUC_{inf} (ng*h/mL)	ND	63.7 ± 2.14 (n = 3)	214 ± 58.3 (n = 3)	355 ± 44.3 (n = 5)	710 ± 164 (n = 2)
C_{max} (ng/mL)	0.537 ± 0.0931 (n = 6)	1.53 ± 0.0935 (n = 6)	4.84 ± 0.706 (n = 6)	8.58 ± 1.11 (n = 6)	19.0 ± 3.55 (n = 3)
t_{max} (hours)	7.33 ± 1.33 (n = 6)	5.33 ± 0.99 (n = 6)	5.00 ± 0.86 (n = 6)	10.67 ± 2.72 (n = 6)	6.00 ± 2.00 (n = 3)
$t_{1/2}$ (hours)	ND	23.3 ± 1.70 (n = 3)	28.8 ± 1.28 (n = 3)	26.0 ± 1.17 (n = 5)	22.8 ± 3.96 (n = 2)

Abbreviations: AUC_{inf} = area under the curve at infinity; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; h = hour(s); mg = milligram(s); ND = not determinable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SEM = standard error of the mean; $T_{1/2}$ = elimination half-life; T_{max} = time to maximum concentration.
[a] Study Part 1b: Cohort 3 from Part 1a returned to receive a single oral dose of CBP-307 at 0.5 mg under fed conditions.
Source: Final report for Study CBP-307AU001.

For the repeated-dose administration of CBP-307, the C_{max} and AUCs increased with the higher administered dose (Table 2). At the steady-state timepoint on Day 28, the median CBP-307 t_{max} was 4 to 6 hours. The average $t_{1/2}$ was similar, ranging 44 to 49 hours, and there were no dose-dependent changes in $t_{1/2}$ within the dose range. The $t_{1/2}$ was slightly prolonged after repeated-dose administration when compared with that after a single-dose administration. Moderate accumulation of CBP-307 (approximately 3 times the levels

following a single dose) was noted in plasma after QD administration for 14 consecutive days.

Table 2: Pharmacokinetics Parameters in the Multiple-Dose CBP-307 Regimen (Study CBP-307AU001)

Multiple-Dose Regimen PK Parameters	Multiple-Dose Cohort 1 CBP-307 Dosing, mg (± SD) (n)		Multiple-Dose Cohort 2 CBP-307 Dosing, mg (± SD) (n)	
	Day 1 0.1	Day 28 0.25	Day 1 0.15	Day 28 0.15
AUC_{0-24} (ng*h/mL)	24.5 ± 3.26 (n = 5)	125 ± 12.4 (n = 4)	26.3 ± 7.45 (n = 5)	79.7 ± 27.3 (n = 6)
AUC_{last} (ng*h/mL)	NA	203 ± 21.9 (n = 4)	NA	131 ± 44.7 (n = 6)
C_{max} (ng/mL)	1.45 ± 0.214 (n = 5)	6.30 ± 0.588 (n = 4)	1.32 ± 0.422 (n = 6)	4.23 ± 1.45 (n = 6)
t_{max} (hours)	6.80 ± 1.50 (n = 5)	6.50 ± 1.50 (n = 4)	5.00 ± 0.68 (n = 6)	4.33 ± 0.33 (n = 6)

Abbreviations: AUC_{0-24} = area under the curve from time 0 to 24 hours; AUC_{last} = area under the curve at the last time point; C_{max} = maximum concentration; mg = milligram(s); NA = not applicable; ng/mL = nanogram(s) per milliliter; PK = pharmacokinetic; SD = standard deviation; T_{max} = time to maximum concentration.
Source: Final report for Study CBP-307AU001.

1.3. Overview of Moxifloxacin

Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic that binds to and inhibits the hERG IKr α subunit and causes a mean increase of the QTc interval of 6 ms after a single 400-mg oral dose. Moxifloxacin is commonly used as a positive control in thorough QT (TQT) studies to satisfy the requirements of International Council for/Conference on Harmonisation (ICH) E14.

Refer to the regional manufacturer package insert of AVELOX (moxifloxacin hydrochloride) tablets for additional information.[2]

1.4. Study Rationale

Regulatory guidance (ICH E14) has emphasized the need to obtain clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase 1, 2, and 3 trials may be conducted they usually have an insufficient sample size, infrequent sampling of ECG data, or the use of inadequate controls to overcome the high rate of spontaneous change in QTc duration. This has resulted in regulatory guidance recommending a dedicated or thorough trial to define the ECG effects of new drugs.

This study will be done in healthy subjects to eliminate variables known to have an effect on ECG parameters (concomitant drugs, diseases, etc.). A supratherapeutic dose of CBP-307 is required to mimic the exposure in healthy subjects that may occur in the target population under the worst of circumstances (eg, concomitant use of cytochrome P450 [CYP]3A4

inhibitor, concomitant liver disease, presence of heart disease, taking more than the clinical dose prescribed) and to allow for PK to QTc modeling to assess the effect of drug concentration on cardiac repolarization.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from the collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with CBP-307 may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic CBP-307 plasma concentrations on the heart-rate corrected QT interval (QTc) in healthy subjects.

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect a small QT effect using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic multiple oral doses of CBP-307 in healthy subjects.
- To assess the PK of CBP-307 following administration of therapeutic and supratherapeutic multiple oral doses in healthy subjects.
- To evaluate the effects of therapeutic and supratherapeutic multiple oral doses of CBP-307 on HR, PR and QRS intervals, and T-wave morphology.

2.2. Endpoints

2.2.1. Electrocardiogram Endpoints

2.2.1.1. Primary

The primary endpoint is the change-from-baseline QTcF (ΔQTcF).

2.2.1.2. Secondary

The secondary endpoints are:

- Change-from-baseline HR, PR, QRS (ΔHR, ΔPR, and ΔQRS);

- Placebo-corrected change-from-baseline HR, QTcF, PR, and QRS (ΔΔHR, ΔΔQTcF, ΔΔPR, and ΔΔQRS);
- Categorical outliers for QTcF, HR, PR, and QRS;
- Frequency of treatment-emergent changes of T- wave morphology and U-wave presence.

2.2.2. Pharmacokinetic Endpoints

Pharmacokinetic parameters of CBP-307 will be determined if data allows:

- area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf})
- area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})

Other PK parameters may also be reported.

2.2.3. Safety Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, randomized, double-blind, double-dummy, placebo-controlled, positive-controlled, single-site, 3-arm study to investigate the effects of therapeutic and supratherapeutic oral doses of CBP-307 on the QTc interval in healthy male and female subjects.

Potential subjects will be asked to read and sign an informed consent form (ICF). After informed consent is obtained, screening procedures and tests to establish subject eligibility to enter the study will be performed within 28 days before Day 1. After informed consent has been obtained but prior to the initiation of study treatment administration, only SAEs will be reported. After placebo administration to all subjects on Day -1, all AEs, whether

volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (ie, from Day -1 until the end of the study).

In this study, approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Randomized subjects will receive the assigned study drug as a single dose in the morning on Days 1, 2 to 5, 6 to 14, and on Day 15 (placebo will be administered to all subjects on Day -1).

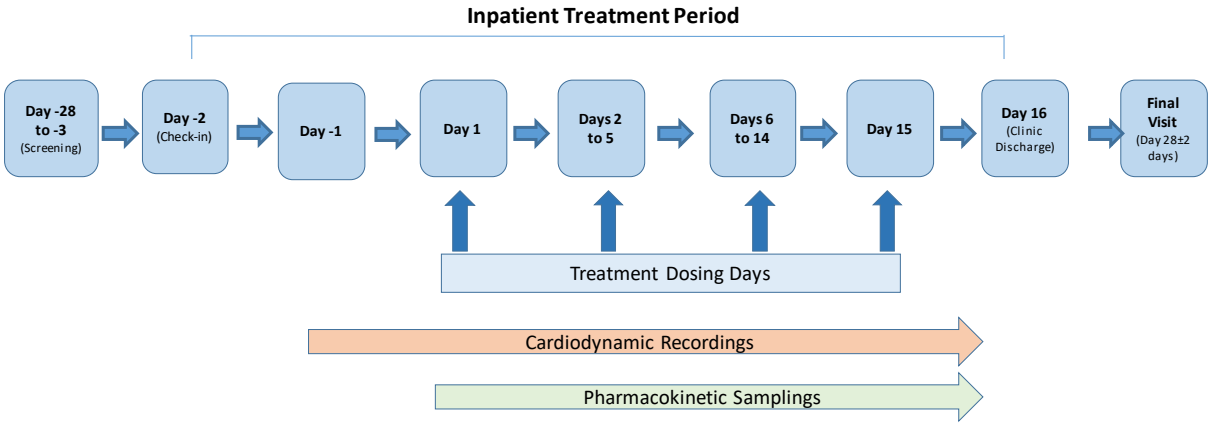
The following treatments will be administered:

- A starting dose of CBP-307 for titration (0.1 mg, Day 1)
- A therapeutic dose of CBP-307 (0.2 mg, Days 2 to 5)
- A supratherapeutic dose of CBP-307 (0.5 mg, Days 6 to 14)
- Placebo (matched to moxifloxacin and CBP-307)
- Moxifloxacin (400 mg)

Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study with an expected peak QT effect (placebo-corrected change-from-baseline QTcF; ΔΔQTcF) of 10 to 15 msec.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects. Subjects will be randomized to receive a treatment sequence that includes 4 treatments (CBP-307 therapeutic dose, CBP-307 supratherapeutic dose, moxifloxacin, or placebo [matched to CBP-307 or moxifloxacin]); assigned study treatments will be administered on Day 1, Days 2 to 5, Days 6 to 14, and Day 15. Dosing details are provided in Table 3.
Blood samples for pharmacokinetic analysis will be collected predose and at each postdose cardiodynamic electrocardiogram timepoint.
An end-of-study visit will occur on Day 28±2 days.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to the first dose administration. Subjects will be admitted into the study site on Day -2 and will remain at the study site until discharge on Day 16. Treatment administration will occur on Days 1, 2 to 5, 6 to 14, and 15 under fasting conditions (all subjects will receive placebo on Day -1). Continuous cardiodynamic ECG monitoring and recording will begin at least 25 hours prior to the administration of study treatments on Day 1 and continue through 24 hours after the administration of study treatments on Days 1, 5, 14, and 15 and at corresponding timepoints on the day before dosing, ie, Day -1. Blood samples for PK analysis will be collected predose and at each postdose cardiodynamic ECG timepoint. Subjects will return to the study site for a follow-up visit on Day 28±2 days.

Baseline for the primary analysis will be determined from predose timepoints collected for 25 hours on Day -1 (prior to administration of study treatments on Day 1). Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Days -1, 1, 5, 14, and 15. The recording will be started 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. Pharmacokinetic blood samples will be collected at the following timepoints: prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15; sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose). Subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each cardiodynamic ECG extraction timepoint, which will end immediately prior to the PK sampling. When timepoints for ECG extraction, safety ECGs, vital sign measurements, and blood draws coincide, procedures will be performed in said order. At each timepoint, up to 10 ECG replicates will be extracted from a 5-minute time window (the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position). The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be evaluated using ECG data collected on Days -1, 1, 14, and 15.

The central ECG laboratory (eResearch Technology Inc., Philadelphia, PA) will be blinded to treatment. The continuous 12-lead digital ECG data will be exported from the system and sent to the central ECG laboratory for review. Resting ECGs to be used in the analyses will be selected from predetermined timepoints specified above and will be read by the central ECG laboratory.

Safety assessments including AEs, vital signs, clinical laboratory tests, safety 12-lead ECGs, and physical examination findings will be performed at screening and at specific timepoints during the study, and/or at the follow-up visit.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 58 days.

The start of the study is defined as the date the first subject signs an ICF. The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 6.

3.2. Discussion of Study Design

The purpose of this study is to evaluate the potential for CBP-307 to cause QT prolongation. As CBP-307 exposure affects heart rate, the primary endpoint for this study will be the QTcF.

The study will be randomized and double-blind because randomization eliminates confounding by baseline variables and blinding eliminates confounding by co-interventions, thus eliminating the possibility that the observed effects of the intervention are because of differential use of other treatments.

The sample size for this study is based on a formal statistical power calculation.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. Both male and female subjects will be included to eliminate similar known ECG variability effects.

Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Pharmacokinetic assessments of CBP-307 concentrations in plasma will be evaluated during the study. The timepoints for the PK sample collections are based on previous studies and are considered adequate to allow for the characterization of the drug's PK after oral dosing. Furthermore, the chosen PK sample collection for CBP-307 is anticipated to be sufficient to allow reasonable estimation of $t_{1/2}$ during the terminal elimination phase.

3.3. Selection of Doses in the Study

According to ICH E14, the highest therapeutic dose and a supratherapeutic dose are recommended for the QT/QTc study. The CBP-307 doses of 0.2 and 0.5 mg were chosen for evaluation in this study based on observed PK results in completed Phase 1 studies. To carefully monitor safety following the administration of CBP-307 doses in Group 1, CBP-307 doses will be up-titrated as follows: subjects will receive a starting dose of 0.1 mg CBP-307 on Day 1 followed by an up-titrated dose of 0.2 mg on Days 2 to 5. Prior clinical experience with CBP-307 has not demonstrated clinically significant abnormalities in laboratory test results in the majority of subjects or a dose-response relationship for safety based on AEs.

A single dose of 0.5 mg is the planned supratherapeutic dose, which balances the characteristics of the study design with the safety of healthy subjects. Testing of CBP-307 at substantial multiples of the anticipated maximum therapeutic exposure is not clinically warranted due to the known safety and tolerability profile of CBP-307.

Further details are provided in the IB.[1]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index between 18.0 and 30.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at screening and confirmed at check-in as assessed by the investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4. Negative pregnancy test for females of childbearing potential at screening (blood test) and check-in (urine test);
5. Supine diastolic blood pressure between 60 and 90 mmHg and systolic blood pressure between 90 and 140 mmHg (inclusive) at screening on a single measurement (confirmed by a single repeat, if necessary) following at least 5 minutes of rest;
6. No clinically significant history or presence of ECG findings as judged by the investigator at screening and check-in, including each criterion as listed below:
    a. Normal sinus rhythm (HR between 60 bpm and 100 bpm inclusive);
    b. QTcF interval ≤450 msec for males and ≤470 msec for females;
    c. QRS interval ≤110 msec; and confirmed by manual over-read if >110 msec.
    d. PR interval ≤200 msec.
7. Has serum potassium, calcium, and magnesium levels within the normal reference range at screening, as judged by the investigator.
8. Able to swallow multiple tablets (based on subject's verbal confirmation).
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Subject is mentally or legally incapacitated or has had significant history of recent mental health issues requiring medication and/or hospitalization at the time of the screening visit or expected during the conduct of the study.
2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the

investigator (or designee). *Note: Childhood asthma that is considered recovered or seasonal allergies that are not currently active or requiring treatment are allowed.*

3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
4. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
5. History of significant multiple and/or severe allergies (eg, latex allergy, band-aids, adhesive dressing, or medical tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.
6. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs within 6 months prior to the first dose of study drug (uncomplicated appendectomy and hernia repair will be allowed).
7. History or presence of:
    a. Hypokalemia, in the opinion of the investigator (or designee);
    b. Risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
    c. Sick sinus syndrome, second, or third degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities;
    d. Repeated or frequent syncope or vasovagal episodes;
    e. Hypertension, angina, bradycardia, or severe peripheral arterial circulatory disorders.
8. Clinically significant abnormalities (as judged by the investigator in laboratory tests results [out-of-range results confirmed on repeat]), including but not limited to the following parameters:
    a. alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin greater than 1.5 × upper limit of normal;
    b. hemoglobin <10 g/dL, WBC <3.0 $\times 10^9$/L, neutrophils <1.5 $\times 10^9$/L, lymphocytes <0.8 $\times 10^9$/L and platelets <100 $\times 10^9$/L or >1200 $\times$ 10^9/L;
9. History or evidence of alcoholism or drug/chemical abuse within 2 years prior to check-in.
10. Alcohol consumption of >10 units per week for males and females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
11. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in.
12. Positive hepatitis panel, positive syphilis test, and/or positive human immunodeficiency virus test (Appendix 2).

13. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 28 days prior to the first dose of study treatment on Day 1. The 28-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
14. Participation in a previous clinical study where subjects received CBP-307.
15. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 28 days prior to first dose of study treatment on Day 1.
16. Use or intend to use any prescription medications/products within 14 days prior to first dose of study drug (Day 1) and throughout the study, unless deemed acceptable by the investigator (or designee). *Note: For females only, the use hormonal contraception, hormone replacement therapy or oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives within 14 days prior to Day 1 is not acceptable, except for Mirena®.*
17. Use or intend to use any drugs known to be significant inhibitors or inducers of CYP enzymes and/or P-gp, including St. John's Wort, for days prior to the first dose of study drug and throughout the study. Appropriate sources will be consulted by the investigator or designee to confirm the lack of PK/PD interaction with the study drug.
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
19. Use or intend to use any nonprescription medications/products including antacids, vitamins (especially those containing magnesium, aluminum, iron, or zinc), minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee).
20. Use of tobacco- or nicotine-containing products within 3 months prior to check-in, or positive cotinine at screening or check-in.
21. Has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for whatever reason), in the opinion of the investigator, within the 28 days prior to the first dose of study treatment, and throughout the study.
22. Consumption of caffeine/xanthine-containing foods or beverages within 48 hours prior to check-in until discharge.
23. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
24. Receipt of blood products within 2 months prior to check-in.
25. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
26. Poor peripheral venous access.
27. Subjects who, in the opinion of the investigator (or designee), should not participate in this study.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Eligible subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). The screening number will be used on all safety samples throughout the study. Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by screening identification number or subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw their informed consent from the study at any time or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, or the inability of the subject to comply with the protocol-required visits or procedures. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the investigator and the sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- investigator decides to terminate the study due to safety concerns such as AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development
- sponsor requests for termination (eg, due to financial or management reasons, etc.) under the premise to fully protect the safety and rights of subjects
- health authority or ethics committee (EC) orders the termination of the trial for any reason.

Definition of end-of-treatment and end-of-study

- end-of-treatment is completion of safety follow-up or withdrawal from the study. End-of-study is the last visit by the last subject.

5. STUDY TREATMENTS

Study treatments are defined as any investigational product (IP), non-investigational product (non-IP), placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, IP and non-IP are referred to as IMP and non-IMP, respectively.

5.1. Investigational Products

The details regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 will be provided in a separate document. Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Table 3: Study Treatments

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
Dosage Formulation		Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)/Level(s)		0.1 mg	Not applicable	400 mg	Not applicable
Dosage Frequency					
Day -1	Group 1		1 capsule		
	Group 2A		1 capsule		
	Group 2B		1 capsule		
Day 1	Group 1	1 × 0.1 mg			1 tablet
	Group 2A		1 capsule	1 × 400 mg	
	Group 2B		1 capsule		1 tablet
Days 2 to 5	Group 1	2 × 0.1 mg			
	Group 2A		2 capsules		
	Group 2B		2 capsules		
Days 6 to 14	Group 1	5 × 0.1 mg			
	Group 2A		5 capsules		
	Group 2B		5 capsules		
Day 15	Group 1				1 tablet
	Group 2A				1 tablet
	Group 2B			1 × 400 mg	
Route of Administration		Oral	Oral	Oral	Oral
Accountability		The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's electronic case report form (eCRF).	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.	The quantity administered, date administered, and lot number of investigational product is to be recorded on each subject's eCRF.
Dosing Instructions		Treatments will be administered after the	Treatments will be administered after the	Treatments will be administered after the	Treatments will be administered after the

Study Treatment Name	Treatment Group	CBP-307	CBP-307 Matched Placebo	Moxifloxacin (Avelox[2])	Moxifloxacin Matched Placebo
		completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.	completion of all predose procedures and after a fast of at least 10 hours with approximately 240 mL of room temperature water.

All supplies of the IMP, both bulk and subject-specific, will be stored in accordance with the manufacturer's or pharmacy's instructions. Until dispensed to the subjects, the study treatments will be stored at the study site in a location that is locked with restricted access.

5.2. Study Treatment Administration

Each dose of study treatment (CBP-307, placebo, or moxifloxacin) will be administered orally following an overnight fast of at least 10 hours, with approximately 240 mL of room temperature water. Additionally, because food has been shown to alter the PK of CBP-307, subjects will be fasted at least 10 hours prior to dose administration and remain fasted for 4 hours postdose on the days when PK samples are collected.

Subjects will be dosed in numerical order while sitting or standing but not be permitted to lie supine for 2 hours after treatment administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.3. Randomization

This is a double-blind randomized study. Subjects will be randomized to one of the treatment sequences before administration of the first dose of study treatment. A randomization list will be generated by a statistician using a computer-generated pseudo-random permutation procedure. The randomization date is to be documented in the subject's medical record and on the enrollment eCRF. A computer-generated randomization schedule and emergency code-break envelopes will be provided to the study site. Randomization details will be included in the randomization specification.

5.4. Blinding

This is a double-blinded study. The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to CBP-307 or moxifloxacin.

- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

- Interim bioanalytical data will be provided to Covance Early Clinical Biometrics in a blinded manner.

To maintain the blind, the investigator will be provided with a sealed randomization code for each subject, containing coded details of the treatment. These individually sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended code-break with the sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until the completion of the study.

At the completion of the study, all unused study treatments (CBP-307, moxifloxacin, placebo-matched CBP-307, and placebo-matched moxifloxacin) will be disposed of by the study site’s pharmacy (RAH Pharmacy), per the sponsor’s written instructions. If destruction is authorized to take place at the study site’s pharmacy, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. All study drug destructions must be adequately documented.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from the use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the investigator (or designee) and/or sponsor have given their prior consent. Medications taken within 28 days before study treatment administration will be documented as a prior treatment. Treatments taken after study treatment administration will be documented as concomitant treatments.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for the treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Females will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives (with the exception of Mirena®) during the study until the follow-up visit (See Appendix 4).

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before the collection of blood samples for clinical laboratory evaluations.

On the days with PK assessments (Appendix 6), the subjects will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 1 hour postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, subjects may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up visit on Day 28±2 days.

Consumption of caffeine/xanthine-containing foods and beverages will not be allowed from 48 hours before check-in until discharge on Day 16.

Consumption of alcohol will not be permitted from 72 hours prior to check-in until discharge on Day 16 and alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not at the study site, from screening to 72 hours prior to the follow-up visit on Day 28±2 days.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to check-in until the follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before check-in until the follow-up visit (Day 28±2 days) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- continuous ECG extraction window
- pharmacokinetic blood samples
- safety assessments
- any other procedures.

This study includes a screening period (Day -28 to Day -2), a treatment period (Days -1 to 16), and a follow-up period (Day 28 ±2 days).

The defined abnormal vital sign measurements (Exclusion Criteria #4) at check-in (Day -2) or baseline (Day -1 predose) will only be considered exclusionary if judged applicable by the investigator. For confirmation of enrollment eligibility based on pulse rate, the pulse rate assessed by vital signs, rather than the 12-lead ECG, will be used. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

7.1. General Assessments

7.1.1. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.1.2. Medical History

At the timepoint specified in Appendix 6, the investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions and any events occurring prior to the first dose of study treatment. All findings will be recorded on the medical history eCRF.

7.2. Electrocardiography Assessments

7.2.1. Continuous 12-lead Electrocardiogram Recording

Continuous 12-lead digital ECG recording will be performed as specified in Appendix 6. All ECG data will be collected using a Holter (or Mortara Surveyor) ECG continuous 12-lead digital recorder. The 12-lead Holter (or Mortara Surveyor) ECG equipment will be supplied and supported by ERT (eResearch Technology Inc., Philadelphia, PA). The continuous 12-lead digital ECG data will be stored onto SD memory cards.

The ECGs to be used in the analyses will be selected by predetermined timepoints as defined in Appendix 6 and will be read centrally by ERT (eResearch Technology Inc., Philadelphia, PA). The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The 12-lead ECGs will be extracted in up to 10 replicates at the predefined timepoints and subjects will be inactive and in a supine position for at least 10 minutes prior to and 5 minutes after each nominal time.

7.2.1.1. TQT Plus Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter (or Mortara Surveyor) recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine, quiet position).

7.2.1.2. Expert Precision QT Analysis

Expert precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc, or RR from beat-to-beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final QC assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR values from each extracted replicate will be calculated, and then the mean of all available medians from a nominal timepoint will be used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS interval of the ECG (QRS) intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed (ie, changes not present at baseline). For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in any replicate at the timepoint. For baseline, the category will be deemed as present if observed in any replicate from all timepoints that constitute baseline.

7.2.2. Safety 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria applies:

- QT interval corrected for HR using Fridericia's method (QTcF) is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.3. Pharmacokinetic Assessments

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 × 3 mL for CBP-307 and moxifloxacin assays) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.3.2. Analytical Methodology

Plasma concentrations of CBP-307 and moxifloxacin will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

7.4. Safety and Tolerability Assessments

7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF until the follow-up visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the study site and each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of placebo administration to all subjects (Day -1) until study completion. If AEs that occur in the screening prior to placebo administration to all subjects (Day -1) are considered to be related to the study procedure, they should be also collected. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an investigator's (or designee's) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2.

A serum qualitative pregnancy or urine test (females only) and follicle-stimulating hormone test (postmenopausal females only) will be performed at the timepoints specified in Appendix 6. A positive urine pregnancy test will be confirmed with a serum pregnancy test. All pregnancies should be reported as specified in Appendix 1.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. At the discretion of the investigator, clinically significant clinical laboratory assessments may be confirmed by repeat sampling. If the clinical significance is confirmed, subjects will be excluded from

participation or, if already included, will be followed until normalization of the test result or for as long as the investigator considers necessary.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.4.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and tympanic temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly. For all subjects, the screening, check-in, or baseline blood pressure, pulse rate, and respiratory rate may be repeated after 5 to 10 minutes if the initial reading is believed to be atypical for the subject.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.4.4. Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Physical examinations include general appearance, head, eyes, ears, nose, and throat, neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, skin, and others.

Height, weight, and body mass index will be assessed at screening.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 64 healthy subjects (at least 30% for each sex) will be randomized into 2 groups (Group 1 and 2) with 32 subjects in each. Group 2 consists of 2 sub-groups (Group 2A and 2B) and each sub-group will be randomized with 16 subjects.

Sample Size for Primary Analysis:

A sample size of 28 evaluable subjects per treatment group will provide more than 94.4% power to exclude that CBP-307 causes more than 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QT effect (ΔΔQTcF) at the observed geometric mean C_{max} of CBP-307 in the study. This power is estimated approximately using a 2-sample t-test. The calculation assumes a 1-sided 5% significance level, an underlying effect of CBP-307 of 3 msec and a

standard deviation (SD) of the ΔQTcF of 8 msec for both CBP-307 and placebo treatment groups. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed-effects model. The concentration-QTc analysis method is supported by Darpo et al 2015[3] and Ferber et al, 2015,[4] and consistent with the experiences from 25 recent TQT studies.

Sample Size Considerations for Assay Sensitivity:
To demonstrate assay sensitivity with concentration-QTc analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (ie, the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTcF] should exceed 5 msec). In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 msec. The within-subject SD of ΔQTcF in the referred study was 5.4 msec based on the by-timepoint analysis. If the effect of moxifloxacin is assumed to be 10 msec, the SE of 1.24 msec corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.64 required to guarantee a power of at least 95% in a paired t-test situation with a sample size of 28 evaluable subjects. In other words, based on this calculation, a power of at least 95% will be obtained as long as the variability of the ΔQTcF, as measured by its within-subject SD from the by-timepoint analysis, does not exceed 6.9 msec (ie, 128% [= 0.82/0.64] of the 5.4 msec observed in the referred study assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 subjects.[5]

8.2. Analysis Populations

8.2.1. Cardiodynamic Population

The QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose timepoint with a valid ΔQTcF value. The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

The PK/QTc population will include all subjects who are in both the QT/QTc and PK populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the concentration-QTc analysis and assay sensitivity. PK/QTc population will be defined for CBP-307, and for moxifloxacin.

The as-treated principle will be applied to all analysis populations mentioned below.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of investigational product and have evaluable PK data of any of the analytes (CBP-307 and moxifloxacin). A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of investigational product drug (therapeutic and supratherapeutic doses of CBP-307, moxifloxacin, or placebo).

8.3. Cardiodynamic ECG Analyses

Baseline for Cardiodynamic ECG Assessments

Baseline for the assessment of the ECG effect of CBP-307 (CBP 307 in Group 1 versus placebo in Groups 2A and 2B) will be time-matched values on Day -1.

For assay sensitivity in Groups 2A and 2B, the following baselines will be used:

- Group 2A: For moxifloxacin administered on Day 1, baseline will be Day 15, on which subjects are administered placebo. For placebo-correction in this group, placebo values will be derived from Day 14 on which subjects are administered placebo, and baseline will be obtained on Day -1.

- Group 2B: For moxifloxacin administered on Day 15, baseline will be Day 1, on which subjects are administered placebo. For the placebo-correction in this group, Day -1 values will be used as placebo (no treatment) and baseline will be obtained on Day 14.

Concentration-QTc Analysis (Primary Analysis)

The relationship between CBP-307 plasma concentrations and change-from-baseline QTcF (ΔQTcF) will be quantified using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched concentrations of CBP-307 as the exploratory variate (0 for placebo), treatment (active=1 or placebo=0), and time (ie, postbaseline timepoints on Days 1, 5, and 14 categorical) as fixed effects, and a random intercept and slope per subject.[6]

The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the CBP-307 concentration) and the treatment effect-specific intercept will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

For the assessment of the ECG effect of CBP-307 versus placebo, the time term incorporated into the models (both by-time point analysis and concentration-QTc analysis [or assay sensitivity]) includes the single predose timepoint and all postdose timepoints on Days 1, 5, and 14, and Days 1 and 15 for active versus placebo and moxifloxacin versus placebo, respectively. All times are relative to the time of dosing on that day which is considered the first dose for the assay sensitivity analysis. For the analysis of CBP-307 versus placebo, the first dose of study treatment is on Day 1.

The geometric mean of the individual C_{max} values for CBP-307 concentrations for subjects in the active drug groups on each of Days 5 and 14 will be determined, respectively. The predicted effect and its 2-sided 90% CI for placebo-corrected change-from-baseline QTcF

(ΔΔQTcF) (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

To evaluate the adequacy of model fit with respect to the assumption of linearity, the observed ΔQTcF values adjusted by population time effect estimated from the model will be used. These individual placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) values equal the observed individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimated population mean placebo effect at timepoint k (ie, time effect). A decile plot, ie, plot of the deciles of observed concentrations and the mean placebo-adjusted ΔQTcF (ΔΔQTcF) and 90% CI at the median concentration within each decile will be given. The regression line presenting the model-predicted ΔΔQTcF[7] will be added to evaluate the fit of a linear model and visualize the concentration-response relationship. The placebo-adjusted $\Delta QTcF_{i,j}$ equals the individual $\Delta QTcF_{i,j}$ for subject i administered with CBP-307 at timepoint j minus the estimation of time at timepoint j (ie, time effect). Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of PD model (linear versus nonlinear) as follows.

Criteria for Negative QT Assessment

If the upper bound of the 2-sided 90% CI of the predicted QTc effect of ΔΔQTcF at the observed geometric mean C_{max} on Days 5 and 14 as well as clinically relevant plasma levels is below 10 msec (ie, the upper bound of the 2-sided 90% CI at the geometric mean C_{max} <10 msec), it can be concluded that CBP-307 does not cause clinically concerning QT prolongation within the observed plasma concentration ranges.

Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the least squares (LS) mean ΔΔQTcF for each postbaseline timepoint and the mean concentration of CBP-307 at the same timepoints. In addition, hysteresis plots will be given for LS mean ΔΔQTcF and the mean concentrations. If a QT effect (ΔΔQTcF) >10 msec cannot be excluded from the by-timepoint analysis in the active dose groups on Days 5 and 14; and the mean peak ΔΔQTcF effect is observed at the same timepoint in the by-timepoint analysis in the active dose groups on Days 5 and 14; and if the difference (delay) between the time to reach the peak QTc effect (ΔΔQTcF) and peak plasma concentration (t_{max}) in the plot (ΔΔQTcF versus CBP-307) of more than 1 hour is observed in a consistent way for the active dose groups on Days 5 and 14, other concentration-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if this curve shows a counterclockwise loop. A significant treatment effect-specific intercept may also be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals and the random effects, scatter plots of standardized residuals versus concentration and versus fitted values, and box plots of standardized residuals versus nominal

time and versus active treatment will be produced. The scatter plot of standardized residuals versus concentration by locally estimated scatterplot smoothing (LOESS) fitting (ie, locally weighted scatterplot smoothing[8] lines) also will be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[9] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, such as an E-max model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

Assay Sensitivity

Assay sensitivity will be demonstrated by similar concentration-QTc analysis of moxifloxacin data. If the slope of the concentration-QTc (change-from-baseline QTcF) for moxifloxacin is statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 msec at the observed geometric mean C_{max} of the 400-mg dose, assay sensitivity will be deemed to have been demonstrated.

By-Timepoint Analysis

The analysis for QTcF for CBP-307 versus placebo will be based on a linear mixed-effects model with change-from-baseline QTcF (ΔQTcF) as the dependent variable, time (ie, postbaseline timepoints on Days 1, 5, and 14: categorical), treatment (therapeutic dose of CBP-307 and supratherapeutic dose of CBP-307 on Day 14, and corresponding placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postdose timepoints within subjects. If the model with unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "CBP-307 versus placebo" for each day of Days 1, 5, and 14 at each postbaseline timepoint on Days 1, 5, and Day 14, respectively.

The by-time point analysis for QTcF will be also performed for moxifloxacin versus placebo at postbaseline timepoints on Day 1 and Day 15. A linear mixed-effects model will be used with ΔQTcF as the dependent variable and time (ie, postbaseline timepoints on Days 1 and 15: categorical), treatment (moxifloxacin and placebo), sequence (placebo/moxifloxacin or moxifloxacin/placebo), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at postbaseline timepoints for subject within visit. The model will also include a subject-specific random effect. If the model with an unstructured covariance matrix fails to converge, other covariance matrices, such as compound symmetry or autoregressive, will be considered. From this analysis, the LS mean, SE, and 2-sided 90% CIs will be calculated for the contrast "moxifloxacin versus placebo" at each postbaseline timepoint, respectively.

For HR, PR, and QRS intervals, the analysis will be based on the change-from-baseline postdose (ΔHR, ΔPR, ΔQRS). The same (by-timepoint analysis) model will be used as described for QTcF. The LS mean, SE, and 90% CI from the statistical modeling for both

change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

Categorical Analyses

The analysis results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both the number of subjects and the number of timepoints. For categorical outliers, the number (percentage) of subjects as well as timepoints who had increases in absolute QTcF values >450 and ≤480 msec, >480 and ≤500 msec, or >500 msec, and changes from predose baseline of >30 and ≤60 msec, or >60 msec; increase in PR from predose baseline >25% to a PR > 200 msec; increase in QRS from predose baseline >25% to a QRS >120 msec; decrease in HR from predose baseline >25% to an HR <50 bpm; and increase in HR from predose baseline >25% to an HR >100 bpm will be determined. For T-wave morphology and U-wave presence, the analyses will be focused on change from baseline (ie, treatment-emergent changes).

8.4. Pharmacokinetic Analyses

The analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, SD, median, minimum, maximum geometric mean, and geometric coefficient of variation) separately by group. Individual and mean plasma CBP-307 and moxifloxacin concentration versus time data will be tabulated and plotted by dose level. Graphical displays of PK data may be provided as well.

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentration for CBP-307 and moxifloxacin, according to the model independent approach:

- C_{max}
- t_{max}
- AUC_{0-24}
- AUC_{inf}
- apparent terminal elimination rate constant (λ_Z)
- $t_{1/2}$
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Other parameters may be added as appropriate.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the Statistical Analysis Plan.

8.5. Safety Analysis

All AEs will be listed and treatment-emergent AEs will be summarized using the descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

8.6. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication.

Examples of AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving clinically significant abnormal laboratory tests, ECG, etc.)
- Exacerbation of previous condition, including increased incidence and/or severity.

Note: Regarding decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. All AEs will be recorded in the medical records and eCRFs. The investigator (or designee) is to record in detail any AE that occurred to the subject, including: AE diagnosis whenever possible, or signs, symptoms, the start date and time of occurrence, the stop date and time of occurrence, seriousness (ie, whether it is an SAE), severity of AEs, causality assessment, actions taken on the investigational product, other actions (eg, medications/treatments given), and outcomes of AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: 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, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

All SAEs will be collected after subjects sign the informed consent form and throughout the entire study, ie, until the end-of-study as specified in the protocol (or at early termination).

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study treatment and considered by the investigator to be possibly related to the study treatment, will be reported to the sponsor (or designee).

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The investigator will complete an SAE report form and forward it by facsimile or email to Covance APAC Drug Safety and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

All SAEs must be reported immediately (within 24 hours of discovery) to: +61-2-8879-2000

SAE Reporting email: aeintake@covance.com (preferred method)

Covance Safety SAE Reporting Fax Number: 61-2-6100-9788 or 1800-882-203 (toll free)

The responsibilities of Covance APAC Drug Safety include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the safety management plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Covance APAC Drug Safety who will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward them to the EC, Medicines and Healthcare Products Regulatory Agency, principal investigator, and the sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

For SAEs, the active reporting period to sponsor or its designated representative begins from the time that the subject provides informed consent through to the last subject visit.

Nonserious AEs should be collected from the time the subject has taken the placebo dose on Day -1 through the last subject visit. If AEs that occur in the screening prior to the placebo administration to all subjects on Day -1 are considered to be related to the study procedure, they should be also collected.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, the sponsor should be notified within 24 hours of investigator awareness of the event. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting as specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

If the female subject becomes pregnant during the clinical trial and has not yet been dosed with study treatment, she must be withdrawn from the study. If the female subject becomes pregnant during the clinical trial and has been dosed, she must discontinue treatment immediately but may remain on study for safety evaluations. If the partner of a male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should report to the sponsor or designee in a pregnancy report form within 24 hours after investigator awareness and report to the EC in time as per local requirement.

The investigator will follow up on pregnancy outcomes, until not less than 12 months after birth, unless otherwise justified, and will report the outcome to the sponsor and ethics committee.

If any adverse pregnancy outcome (eg, the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformations), it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Potassium Sodium Total bilirubin Total protein Urea Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if indicated by dipstick)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen Syphilis	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol Tricyclic antidepressants Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[b] Urine pregnancy test[b] **Other Tests** Low density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (on Day 28±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including serology, syphilis, follicle-stimulating hormone, and serum pregnancy tests)	12.5	5	62.5
CBP-307/Moxifloxacin Pharmacokinetics (includes discard volume per draw)	8	40	320
Total:			382.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Females on hormone replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the investigator.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the follow-up visit. Primary (non-barrier) methods of contraception include:

- surgical method performed at least 3 months prior to the screening visit:
  - bilateral tubal ligation or bilateral salpingectomy
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- non-hormonal intrauterine device or Mirena® (other hormonal intrauterine devices will not be allowed) in place for at least 3 months prior to the first dose of the study drug
- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom without spermicide
- female condom without spermicide
- cervical cap without spermicide (as prescribed)
- diaphragm without spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from check-in (Day -2) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom without spermicide) in addition to a second method of acceptable contraception from check-in until 90 days after the follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- cervical cap without spermicide
- diaphragm without spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a

subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol, local legal and regulatory requirements and with the following:

- General principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the human research ethics committee (HREC) by the investigator and reviewed and approved by the HREC before the study is initiated.

Any protocol amendments will require EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the HREC. All correspondence with HREC should be retained in the investigator file. A copy of HREC approval should be forwarded to the sponsor.

- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of SAEs or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the EC, and all other applicable local regulations.

Regulatory Authority

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following the discussion of the study with study site personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed as follows:The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all

manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 6: Schedule of Assessments

Schedule of Assessments

Study Period	Screening	In-house Treatment Period									End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2 to 4**	**5**	**6 to 13**	**14**	**15**	**16**	**28±2**
Informed consent	X										
Eligibility criteria review (Inclusion/Exclusion)	X	X									
Demographics	X										
Medical history	X										
Admission to clinical research unit[1]		X									
Discharge from clinical research unit[2]										X	
Randomization				X							
Vital signs[3,8]	X	X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X										
Physical exam	X	X									X
Hematology	X	X				X				X	X
Clinical chemistry (including cholesterol panel tests)	X	X				X				X	X
Urinalysis	X	X								X	X
Serology for HIV-1/HIV-2 antibodies and p24 antigen, HBsAb, HBcAb, HBsAg, or HCVAb	X										
12-lead safety electrocardiogram[4,8]	X	X	X	X	X	X	X	X	X	X	X
Breath alcohol, urine drug toxicology and cotinine	X	X									
Cardiodynamic monitoring (Holter)/replicate ECG extraction[5]			X	X		X		X	X		
Pregnancy test[6]	X	X									X

Schedule of Assessments

Study Period	Screening	In-house Treatment Period									End-of-Study/Follow-up Visit
Study Day(s)	**-28 to -3**	**-2**	**-1**	**1**	**2 to 4**	**5**	**6 to 13**	**14**	**15**	**16**	**28±2**
Follicle -stimulating hormone test (postmenopausal females only)	X										
CBP-307/placebo administration			X	X	X	X	X	X			
Moxifloxacin/placebo administration				X					X		
Blood sampling for PK[7,8]				X		X		X	X		
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; PK = pharmacokinetic.

1. Subjects will be asked to arrive at the clinical site in the afternoon 2 days before start of dosing on Day 1 (Day -2).
2. Discharge from unit will occur after the 24-hour PK samples and after completion of safety assessments on Day 16.
3. **Screening and Check-in on Day -2:** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure. **Other days (except for Day 16):** Prior to and 2 hours after dosing, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **Discharge (Day 16):** Prior to discharge, supine vital signs (tympanic temperature, pulse rate, respiratory rate, and blood pressure). **End of Study/Follow-up Visit (Day 28±2 days):** Tympanic temperature, respiratory rate, and supine pulse rate and blood pressure.
4. 12-lead safety ECG will be recorded in triplicates before dosing and in singles 2 hours postdose on all study days and before discharge on Day 16. Postdose safety will be interpreted on-site by the investigator and may be repeated to confirm/refute clinically abnormal findings.
5. Continuous cardiodynamic monitoring (Holter) will be performed for 25 hours on Day -1 (baseline), 1, 5, 14, and 15. The recording will be started at least 1 hour before dosing and at the corresponding clock time on Day -1. Replicate 12-lead ECGs will be extracted from the continuous recording prior to dosing (-30 minutes) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on each day. At timepoints for ECG extractions, subjects will be supinely resting in an undisturbed environment. When timepoints for ECG extraction, safety ECGs, vital signs assessment, and blood draws coincide, procedures will be performed in this order. The ECG effects of CBP-307 will be tested on data from Day -1 (baseline for both groups), Day 5 (therapeutic concentrations versus placebo), and Day 14 (supratherapeutic concentrations versus placebo). Assay sensitivity with moxifloxacin will be tested on data from Days -1, 1, 14, and 15.
6. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Day -2 and at the follow-up visit (Day 28±2 days). A positive urine pregnancy test will be confirmed with a serum pregnancy test.
7. Pharmacokinetic samplings will be performed prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing on each PK sampling day (Days 1, 5, 14, and 15).
8. Allowable assessment/sample collection windows are as follows: ±2 minutes for 0.5 hours postdose, ±5 minutes for 1 to 4 hours postdose, ±10 minutes for 6 to 8 hours postdose, and ±30 minutes for 12 to 24 hours postdose.