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NCT Number:	NCT05293171
Sponsor Study Number:	BL-8040.TQT.103
Official Study Title:	Single-Dose, Randomized, Double-Blind, Placebo-Controlled, Positive-Controlled, Four-Way Crossover Study to Investigate the Effect of BL-8040 (Motixafortide) on the QTc Interval in Healthy Subjects
Document Version and Date:	Clinical Study Protocol, Amendment 2, 30 June 2021

[redacted]

BIOLINERX

Clinical Protocol

A Single-Dose, Randomized, Double-Blind, Placebo-Controlled, Positive-Controlled, Four-Way Crossover Study to Investigate the Effect of BL-8040 (Motixafortide) on the QTc Interval in Healthy Subjects

[redacted] **Project No.: CA33565**

Sponsor Project No.: BL-8040.TQT.103

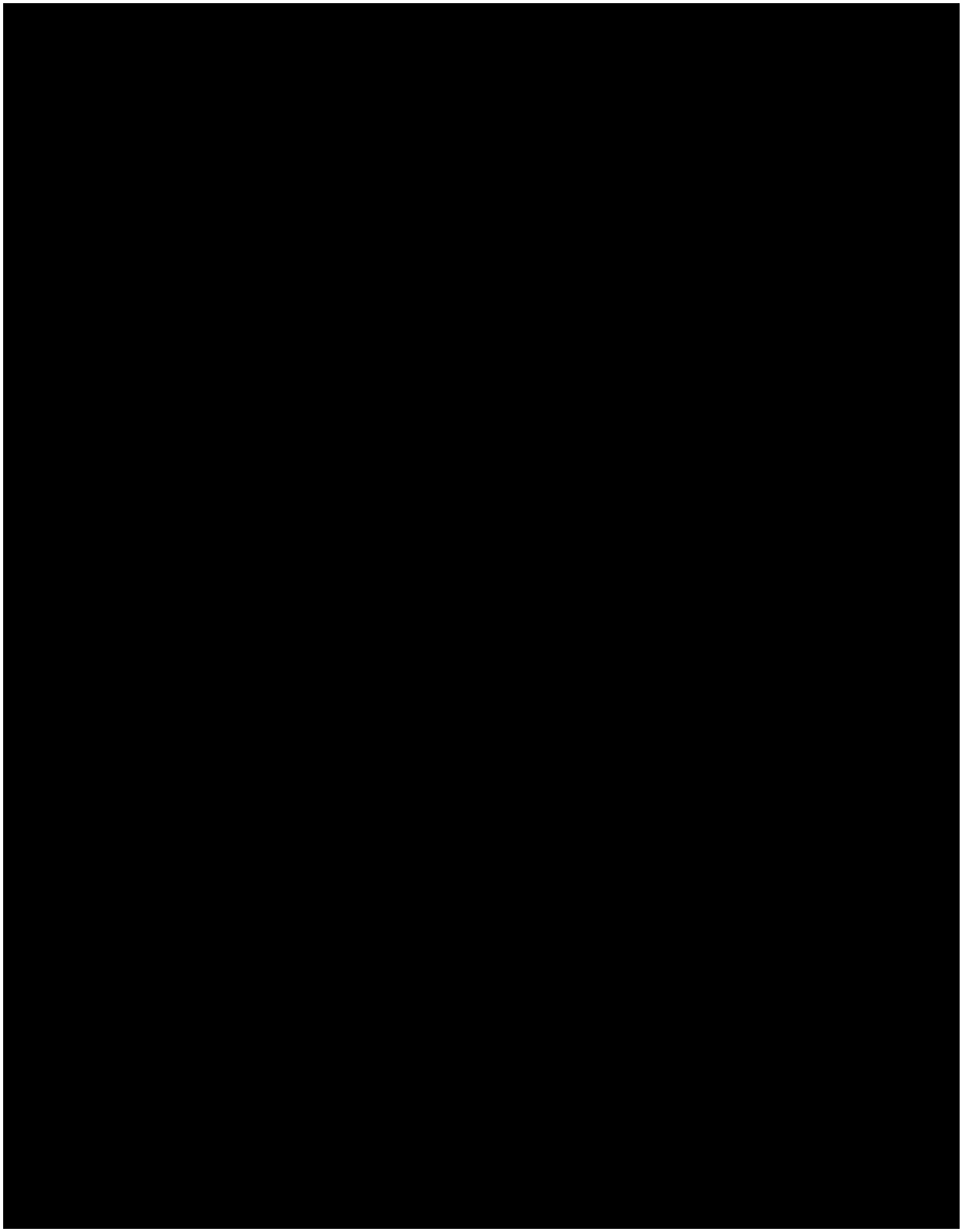
US IND No.: [redacted]

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY



2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Single-Dose, Randomized, Double-Blind, Placebo-Controlled, Positive-Controlled, Four-Way Crossover Study to Investigate the Effect of BL-8040 (Motixafortide) on the QTc Interval in Healthy Subjects

[redacted]

Signature: Date: _____

A Single-Dose, Randomized, Double-Blind, Placebo-Controlled, Positive-Controlled, Four-Way Crossover Study to Investigate the Effect of BL-8040 (Motixafortide) on the QTc Interval in Healthy Subjects

SPONSOR AND SPONSOR'S REPRESENTATIVES:

BioLineRx Ltd.

Date: 30 June 21

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

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5 SYNOPSIS

Compound:	BL-8040 (motixafortide)
Study Title:	A Single-Dose, Randomized, Double-Blind, Placebo-Controlled, Positive-Controlled, Four-Way Crossover Study to Investigate the Effect of BL-8040 (Motixafortide) on the QTc Interval in Healthy Subjects
Study Phase and Type:	Phase I – cardiac liability study
Study Objectives:	**Primary:** To assess the corrected QT (QTc) effects (electrocardiogram [ECG]) of BL-8040 1.25 mg/kg (therapeutic dose) and 2 mg/kg (supratherapeutic dose) following a single subcutaneous (SC) injection relative to placebo in healthy subjects. **Secondary:** • To evaluate the safety, tolerability, and pharmacokinetics (PK) of single therapeutic and supratherapeutic SC injections of BL-8040 in healthy subjects. • To assess the effects of single therapeutic and supratherapeutic SC injections of BL-8040 on non-QT interval ECG parameters (heart rate [HR], RR, PR, and QRS intervals) in healthy subjects. • To evaluate assay sensitivity (i.e., to evaluate the effect of a positive control, a single oral 400 mg dose of moxifloxacin, on the QTc interval in healthy subjects). **Exploratory:** To evaluate the pharmacodynamic (PD) effects of single therapeutic and supratherapeutic SC injections of BL-8040.
Summary of Study Design:	This is a randomized, double-blind (in respect to BL-8040 and BL-8040-matching placebo dosing), placebo- and positive-controlled, 4-period, 4-way crossover study in healthy subjects. A continuous 12-lead cardiodynamic ECG recording will be collected for approximately 24 hours on Day -1 of Period 1 for use in the optimized individual corrected QTc (QTcI) baseline calculations. On Day 1 of Period 1, subjects will be randomized to 1 of 12 treatment sequences. Each treatment sequence comprises 4 treatment periods. On Day 1 of each period, subjects will receive single-dose SC injection of BL-8040 (therapeutic or supratherapeutic dose),

	single-dose SC injection of BL-8040-matching placebo, or a single oral dose of moxifloxacin. Cardiodynamic readings, plasma PK samples, and blood PD samples will be collected at different time points prior to dosing and up to 24 hours postdose in each period, as appropriate. There will be a washout period of 5-7 days between dosing in each period. All subjects who received at least one dose of any study drug (including subjects who terminate the study early) will return to the clinical research unit (CRU) 7 ± 2 days after the last dose for follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit.
Number of Subjects:	Approximately 40 healthy, adult male and female subjects will be enrolled to ensure at least 26 subjects complete the study. Every attempt will be made to enroll no less than 30% of either gender.
Dosage, Dosage Form, Route, and Dose Regimen:	Subjects will receive each one of the following treatments in a pre-defined order according to the sequence scheme determined at randomization. The sequences to be used in the randomization are detailed in Table 4. Treatments are described as follows: **Treatment A:** (Therapeutic) 1.25 mg/kg BL-8040 + BL-8040-matching placebo administered via SC injection **Treatment B:** (Supratherapeutic) 2 mg/kg BL-8040 administered via SC injection **Treatment C:** (Placebo Control) BL-8040-matching placebo administered via SC injection **Treatment D:** (Positive Control) 400 mg moxifloxacin (1 x 400 mg tablet) administered orally For each subject, an appropriate volume of BL-8040-matching placebo will be used in Treatments A and C such that the total volume administered for each of Treatments A and C will be the same as the total volume injected in Treatment B. All study drugs will be administered on Day 1 following an overnight fast. Moxifloxacin will be administered with approximately 240 mL of water. Hour 0 will be set as the start of dosing.

Key Assessments:	**Cardiodynamics:** The following ECG parameters will be measured and calculated: HR, RR, PR, QRS, QT, QTcI, Fridericia corrected QTc (QTcF), and ECG waveform morphologies. The primary analysis will be based on concentration-QTc modeling of the relationship between plasma concentrations of BL-8040 and change-from-baseline QTcI (ΔQTcI) with the intent to exclude an effect of placebo-corrected ΔQTcI (2-sided 90% upper confidence bound of ΔΔQTcI) > 10 msec at clinically relevant plasma levels. The relationship between BL-8040 plasma concentration and ΔQTcF will be explored. In addition, the effects of BL-8040 on the change-from baseline placebo-corrected QTcI, QTcF, HR, PR, and QRS (ΔΔQTcI, ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will be evaluated at each postdose time point ("by time point" analysis). An analysis of categorical outliers will be performed for changes in QTcI, QTcF, HR, PR, and QRS. Morphologic analyses will be performed on the ECG waveforms. Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔΔQTcI of moxifloxacin using a similar model as for the primary analysis. Assay sensitivity will be deemed as met if the slope of the concentration-QTc relationship/ΔQTcI is statistically significant at 10% level of significance in a 2-sided test and the predicted QT effect (i.e., the lower bound of the 2-sided 90% confidence interval [CI] of ΔΔQTcI) is above 5 msec at the observed geometric mean Cmax of 400 mg moxifloxacin. **Pharmacokinetics:** The following PK parameters will be calculated for BL-8040 and moxifloxacin in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F. PK parameters will be summarized by treatment using descriptive statistics. **Safety:** Safety will be monitored through AEs, 12-lead safety ECGs, vital sign measurements, clinical laboratory tests, and physical examination. AEs will be tabulated and descriptive summary statistics for the 12-lead safety ECGs, vital signs, and clinical laboratory tests will be computed and provided, as appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures [a]	Screening [b]		Study Days for Treatments A, B, and C [c]																	FU [d]
Days →	-30 to -2	-2 [e]	-1	1														2		
Hours →		C-I		-0.75	-0.5	-0.25	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	16 [f]	24	
Administrative Procedures																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Medical History	X																			
Demographics	X																			
Safety Evaluations																				
Full Physical Examination [g]	X																		X [h]	X
Height	X																			
Weight	X	X	X [i]																	
12-Lead Safety ECG	X	X	X [i]										X						X [h]	X
Vital Signs (HR, BP, Respiratory Rate, T)	X	X	X [i]						X				X				X		X [h]	X
Hem, Serum Chem [j], Coag, and UA	X	X	X [i]																X [h]	X
Blood for CBC							X [k]			X			X		X		X	X	X		
Serum Pregnancy Test (females only)	X	X																		X
Serum FSH (postmenopausal females only)	X																			
Urine Drug and Alcohol Screen	X	X																		
Urine Cotinine Screen	X																			
HIV/Hepatitis Screen	X																			
Randomization							X [l]													
AE Monitoring	X	X																		X
Concomitant Medication Monitoring	X	X																		X
Study Drugs Dosing / PK / PD / Cardiodynamics																				
Premedication				X [m]																
BL-8040 or Placebo Dosing							X													
Blood for BL-8040 PK							X [k]	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Moxifloxacin PK (for Potential Analysis)							X [k]					X								
Cardiodynamic 12-lead ECG by Holter [n]			X [o]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]							X [k]			X			X		X		X	X	X	X
[redacted]							X [k]						X		X		X	X		X

Study Procedures [a]	Screening [b]	Study Days for Treatments A, B, and C [c]																	FU [d]
Days →	-30 to -2	-2 [e]	-1	1													2		
Hours →		C-I		-0.75	-0.5	-0.25	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	16 [f]	24	
Other Procedures																					
Confinement in the CRU		X																			
Visit and Return Visit	X																				X

Study Procedures [a]	Screening [b]	Study Days for Treatment D [c]																		FU [d]
Days →	-30 to -2	-2 [e]	-1	1														2		
Hours →		C-I		-0.75	-0.5	-0.25	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	16 [f]	24	
Administrative Procedures																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Medical History	X																			
Demographics	X																			
Safety Evaluations																				
Full Physical Examination [g]	X																		X [h]	X
Height	X																			
Weight	X	X	X [i]																	
12-Lead Safety ECG	X	X	X [i]										X						X [h]	X
Vital Signs (HR, BP, Respiratory Rate, T)	X	X	X [i]						X				X				X		X [h]	X
Hem, Serum Chem [j], Coag, and UA	X	X	X [i]																X [h]	X
Serum Pregnancy Test (females only)	X	X																		X
Serum FSH (postmenopausal females only)	X																			
Urine Drug and Alcohol Screen	X	X																		
Urine Cotinine Screen	X																			
HIV/Hepatitis Screen	X																			
Randomization							X [l]													
AE Monitoring	X	X																		X
Concomitant Medication Monitoring	X	X																		X
Study Drugs Dosing / PK / Cardiodynamics																				
Premedication				X [m]																
Moxifloxacin Dosing							X													
Blood for BL-8040 PK (for Potential Analysis)							X [k]		X											
Blood for Moxifloxacin PK							X [k]		X	X	X	X	X	X	X	X	X	X		X
Cardiodynamic 12-lead ECG by Holter [n]			X [o]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Procedures																				
Confinement in the CRU		X																		
Visit and Return Visit	X																			X

a For details on Procedures, refer to Section 13.

b Within 28 days prior to check-in (Day -2 in Period 1).

c There will be a washout period of 5-7 days between dosing in each period. Each subject will participate for a total for 4 periods.

d All subjects who received at least one dose of any study drug (including subjects who terminate the study early) will return to the CRU 7 ± 2 days after the last dose for follow-up procedures, and to determine if any AE has occurred since the last study visit.

e Subjects will be admitted to the CRU on Day -2 in Period 1, at the time indicated by the CRU, and will remain confined until completion of study procedures on Day 2 of Period 4. Procedures scheduled on Day -2 will only be performed in Period 1.

f The 16-hour postdose on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 2.

g Symptom-driven physical examination may be performed at additional times, at the PI or designee's discretion.

h To be performed at the end of each period or prior to early termination from the study.

i To be performed only in Periods 2, 3, and 4.

j Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of early discontinuation or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.

k To be performed prior to study drug dosing, but after the last baseline cardiodynamic ECG reading.

l In Period 1 only. Subjects will be randomized to 1 of 12 treatment sequences (Table 4).

m Premedication will be administered to all subjects as described in Section 12.1, prior to the first baseline cardiodynamic ECG reading.

n Holter monitors will be used to collect continuous cardiodynamic ECG samples on Day -1 of Period 1 and Day 1 of each period. On Day 1 of each period, ECG recordings will be extracted from the Holter monitor data within a 5-minute time window prior to the PK blood sample collection. Subjects must rest quietly in the supine position for at least 10 minutes prior to the extraction and throughout the duration of the extraction. There should be minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other subjects). When cardiodynamic ECG extractions coincide with 12-lead safety ECGs, vital signs assessment, and blood draws, procedures should be carried out in this order: 12-lead safety ECG, cardiodynamic ECG extraction, and blood sample for PK assessments as close to the exact time point as possible. Vital signs may be performed either before or after blood sample collection.

o To be performed in Period 1 only. Holter monitors will be used to collect a continuous 12-lead cardiodynamic ECG recording for approximately 24 hours on Day -1.

Abbreviations: AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, CBC = Complete blood count, Chem = Chemistry, Coag = Coagulation, CRU = Clinical research unit, ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, PI = Principal Investigator, [redacted], T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

^{14}C	Carbon-14 (radiocarbon)
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AML	Acute myeloid leukemia
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular
BMI	Body mass index
bpm	Beats per minute
°C	Degrees Celsius
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after extravascular administration
cm	Centimeter
Cmax	Maximum observed concentration
CNS	Central nervous system
CRF	Case report form
CRU	Clinical research unit
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
Δ	Change-from-baseline
ΔΔ	Placebo-corrected change-from-baseline
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRF	Dose range finding

ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
h	Hour
HBsAg	Hepatitis B surface antigen
HED	Human equivalent dose
hERG	Human ether-a-go-go related gene
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLM	Human liver microsome(s)
HR	Heart rate
HSC	Hematopoietic stem cell
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
*I*Kr	Rapid delayed rectifier
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LS	Least-squares
µg	Microgram
µL	Microliter
µM	Micromolar
m^2	Meters squared

MATE	Multidrug and toxin extrusion protein
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute(s)
mIU	Milli International Units
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
n	Sample size
ng	Nanogram
nM	Nanomolar
No.	Number
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation transporter
oz	Ounce
PD	Pharmacodynamic(s)
PEPT	Peptide transporter
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Interval from the onset of the P wave to the start of the QRS complex
QA	Quality Assurance
QRS	QRS complex; interval including the Q, R, and S waves
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
QTcF	Fridericia corrected QT interval
QTcI	Optimized heart rate-corrected QT interval
RA	Radioactivity
RNA	Ribonucleic acid
RO	Receptor occupancy

RR	Interval between two successive R waves on the electrocardiogram tracing
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous or subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SOP	Standard operating procedure
SSS	Sum of squared slopes
t½	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum observed concentration
TQT	Thorough-QT
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after extravascular administration
WBC	White blood cell
WHO	World Health Organization

8 INTRODUCTION

8.1 BL-8040 (Motixafortide)

BL-8040 (INN: motixafortide, formerly known as 4F-benzoyl-TN14003 or BKT140 and developed by Biokine Therapeutics Ltd.) is a novel selective inhibitor of the CXCR4 chemokine receptor. BL-8040 is a synthetic peptide that binds and inhibits the CXCR4 chemokine receptor with high affinity (IC_{50} 1-10 nM). BL-8040 has been shown in-vitro and in-vivo to be a specific antagonist of the CXCR4 receptor and to have a slow dissociation rate from the receptor. In in-vivo animal studies, as well as in clinical studies, BL-8040 has demonstrated accelerated mobilization of adult white blood cells (WBCs [neutrophils, monocytes, and lymphocytes]), normal hematopoietic stem-cells, and leukemic blasts (in study performed on acute myeloid leukemia [AML] patients) from the bone marrow to the peripheral blood. In-vitro and in-vivo nonclinical studies have shown that in addition to its activity as a mobilizer of hematopoietic cells, BL-8040 exhibits a CXCR4-dependent preferential anti-tumor effect against malignant cells. In-vivo nonclinical studies have also shown that multiple doses of BL-8040 have led to a marked increase in the number of hematopoietic progenitor cells and HSCs in the bone marrow and peripheral blood of mice. In addition, BL-8040 promoted increased megakaryopoiesis in the bone marrow, leading to increased platelet production with a prolonged effect in-vivo.

More complete details and references for the nonclinical and clinical background sections of this report may be found in the BL-8040 Investigator's Brochure (IB) (IB v8.0, 2020).

BioLineRx is developing BL-8040 for several indications, including the mobilization of HSCs for autologous and/or allogeneic transplantations in subjects undergoing peripheral blood stem cell transplantation, the treatment of patients with hematological malignancies or pre-malignant conditions, the treatment of patients with solid tumors, and the treatment of bone marrow failure diseases.

8.1.1 Nonclinical Pharmacology and Pharmacokinetics

BL-8040 is a synthetic cyclic peptide with molecular formula $C_{97}H_{144}N_{33}O_{19}S_2F$ and average molecular weight of 2160 Daltons. The antagonistic effects of BL-8040 on the CXCR4 chemokine receptor were characterized in in-vitro and/or in-vivo systems. BL-8040 inhibited the binding of CXCL12 to CXCR4 and selectively inhibited CXCL12-stimulated cellular activities, such as calcium flux, chemotaxis, binding and hematopoietic. BL-8040 is a potent inhibitor of the CXCR4 chemokine receptor, and induces rapid (0.5-2 hour), dose-dependent, and transient mobilization of WBCs, including monocytes, B cells, T cells, progenitors and HSCs in mice treated with BL-8040 as a single agent. The effect was seen in mice at a dose range of 2.5-10 mg/kg, equivalent to 0.2-0.83 mg/kg, respectively, in humans.

The nonclinical absorption, distribution, metabolism, and excretion (ADME) of BL-8040 has been evaluated in several in-vitro and in-vivo studies. The studies included evaluation of BL-8040 stability in plasma and whole blood, metabolic stability in liver microsomes, drug-drug interaction (DDI) studies (cytochrome P450 [CYPs] and transporters), and protein binding studies. PK/mass balance and metabolite radio-profiling and identification studies

with [^{14}C]-Tyr BL-8040 and [^{14}C]-Nal-BL-8040 were conducted in dogs and rats. Tissue distribution studies were conducted in rats with [^{14}C]-Tyr BL-8040 and [^{14}C]-Nal-BL-8040. Additionally, identification of the metabolic products in the stability assays was performed and the metabolic profiles of toxicology models (rats and dogs) and humans (in-vitro) were compared.

BL-8040 exhibited very high binding to human plasma proteins (99.2%) and high binding to the proteins in rat and dog plasma (94.9% and 96.9%, respectively). Absorption studies of BL-8040 were performed in rats and dogs following SC (the clinical administration route) and/or intravenous (IV) administration (to maximize exposure). PK parameters calculated for BL-8040 following increasing doses injected IV or SC demonstrated a linear kinetic profile. Absorption following SC doses of BL-8040 in dogs was rapid, the elimination half-life (t½) ranged from ~0.36-5.8 hours across several studies. The time to maximum plasma concentrations (Tmax) was generally 1-2 hours with no obvious differences between sex and doses. Plasma exposures were higher after repeated administrations compared to single-dose administration. Accumulation was modest, with approximately 1.5 fold higher Cmax and area under the curve (AUC) after multi-day (28-day) dosing.

Investigation of the ADME properties of BL-8040, and specifically the disposition of unnatural amino acids of BL-8040 was conducted. The initial ADME studies in rats and dogs using [^{14}C]-Tyr BL-8040 resulted in low recovery (overall radioactivity [RA]) excreted in urine and feces was 9% and 12% of the administered RA dose in rat and dog, respectively) of excreted RA. Approximately 21% of administered RA was accounted for expired air in rats. This was probably related to the labeling position at the natural amino acid and likely reflect the rapid digestion of [^{14}C]-Tyr-labelled BL-8040 to the constituent amino acids and incorporation of the radiolabeled natural amino acid into downstream de novo synthesis of other peptides/proteins. In these studies, plasma metabolic profiles observed in rats and dogs were qualitatively and quantitatively similar and represented two major metabolic pathways: catabolism to individual amino acids and catabolism in parallel with mono- and polydeimination (citrullination) of Arginine residues.

None of the circulating individual metabolites exceeded 1.5% of total plasma RA exposure with the exception of labeled Tyr (free amino acid) (66.1% [rat]; 22.1% [dog]) which was cleared quickly through identified pathways. Due to the low recovery of excreted radioactivity obtained with the Tyr-labelled compound the information collected from these studies supported mainly the metabolite profile and identification at the early time points after drug administration, and these studies were therefore complemented with additional studies using ^{14}C-labeled BL-8040 with ^{14}C label in the naphthalene ring at the unnatural amino acid Nal.

Following a single SC administration of radiolabeled [^{14}C]-Nal-BL-8040 the recovery of RA was almost complete in rats and dogs with 97% and 96% of RA excreted in rats and dogs, respectively. Approximately 80% of RA was excreted with urine with no parent drug detected in both species within 96 hours. There was no detectable RA in expired air.

In both rat and dog, no major metabolite (or parent drug) in urine exceeded 30% of total clearance. The total amount of [^{14}C]-Nal-BL-8040-related material excreted in feces as a

percentage of the administered dose was approximately 12.41% and 3.92% in rats and dogs, respectively up to 168 hours postdose. There was no detectable parent drug in feces of either species, and thus biliary excretion of parent drug is assumed to be minimal. Biliary excretion also appears to be only a very minor elimination pathway for BL-8040 metabolites, with cumulative excretion of individual metabolites in feces never exceeding 3.21% and 1.08% of the dose in rat and dog in respectively.

Plasma metabolic profiles observed in rats and dogs following administration of [^{14}C]-Nal-BL-8040 were similar with formation of free Nal (58.6% [rat]; 33.5% [dog]) and its further metabolism via identified metabolic pathways. One of these Nal-derivative metabolites circulating in the plasma, 2-naphthalene-acetic acid, was represented in different levels in rat and dog (7.5% and 55.5%, respectively) and 2 Nal-related metabolites in dog urine were >20% of the dose but were not major species in rat urine.

Together these findings support the position that hepatic or renal impairment will not affect the PK profile of BL-8040. Overall the ADME studies show that BL-8040 is catabolized via hydrolysis and/or disulfide bond cleavage to form smaller peptides, and single amino acids, as expected.

Following a single SC administration of radiolabeled [^{14}C]-Nal-BL-8040 tissue distribution was rapid and widespread in rats with detectable concentrations measured in all tested tissues by 1 hour postdose and, reaching maximum concentrations between 4 and 8 hours postdose. Most tissues were below quantification limit at 840 hours postdose. The injection site, aorta, urinary bladder wall, kidney, pancreas and ocular system contained highest [^{14}C]-Nal-BL-8040-derived distribution of radioactivity at moderate and/or sustained levels (tissue:blood AUC0-t ratios of 1.11 to 42.90). BL-8040 show negligible penetration through the blood-brain barrier.

In-vitro stability study in whole blood and plasma from rat, dog, and human whole blood and plasma suggested that BL-8040 is stable in all three species. Five metabolites (degradation products of BL-8040) were identified following 2 hours of incubation in liver microsomes. The metabolic profiles, as tested in in-vitro using liver microsomes of rat, dog and human, are similar across species, with the exception of 3 minor unique human catabolites that were observed at low levels in this system. However, the liver microsome findings are of less relevance since 1. the main excretion pathway of BL-8040 catabolites is via the kidneys, 2. the catabolism is non-NADPH dependent and 3. drug permeability to the liver is low. Therefore, metabolites formed in blood/plasma ex-vivo better represent the in-vivo elimination profile. Moreover, the inhibitory activity of BL-8040 and two of its minimally proteolyzed human catabolites was tested in vitro using the CXCL12-CXCR4 chemotaxis assay. These catabolites with one or two amino acids cleaved from the C-terminus of BL-8040, exhibited poor to no inhibition of CXCL12-CXCR4 chemotaxis suggesting that further truncated versions of BL-8040 are not expected to exhibit activity.

Evaluation of in-vitro metabolism of BL-8040 in rat, dog, and human liver microsomes (HLM) demonstrated that BL-8040 was moderately metabolized, with 51.9-70.8% remaining following incubation. BL-8040 was found to be a low clearance compound with intrinsic clearance rates from 2.9-6.0 μL/min/mg protein. The disappearance t½ values of BL-8040

ranged from 1.93-3.98 hours. Presence of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) in the incubation samples containing human microsomes had a minor effect on the t½ values of BL-8040, indicating that the majority of the biotransformation was made through NADPH-independent enzymes with a minimal contribution of NADPH-dependent enzymes.

Sixteen metabolites were identified following BL-8040 incubation with rat, dog, and HLM. All were hydrolysis and/or disulfide bond cleavage products of BL-8040 and no other biotransformations were observed. All major metabolites found in human were also identified in animal species. Given that BL-8040 is a peptide (molecular weight = 2160 g/mol) unlikely to reach significant intracellular concentrations in intact hepatocytes (cells that more closely resemble in-vivo conditions compared to liver microsomes), the in-vivo relevance of at least some of the biotransformation products observed following microsomal incubation should be viewed cautiously.

Direct inhibitory effects of BL-8040 on all tested CYPs were observed in pooled HLM with apparent IC_{50} values ranging from 9.3 to 32.4 μM. The inhibitory effects of BL-8040 remained similar after a 30-minute pre-incubation with apparent IC_{50} values ranging from 10.0 to 47.1 μM, indicating that inhibition was not time-dependent. Contrary to HLM, BL-8040 did not cause > 25% inhibition of the activities of CYP isozymes (CYP2B6, 2C8, and 3A4) in human hepatocytes at concentrations as high as 50 μM despite potent inhibition of BL-8040 on these three enzymes (IC_{50} of 9.3-15.3 μM). Inhibition in hepatocytes was lower than microsomes (i.e., less potent) likely due to decreased uptake of BL-8040 into cells. Taking into account plasma protein binding, based on the fact that the expected human Cmax total is < 2 μM and only 1% of BL-8040 is found in the unbound fraction, the in-vitro human hepatocyte results predicts that BL-8040 exhibits a low potential for in-vivo CYP inhibition.

BL-8040 at concentrations of up to 10 μM showed no induction potential for CYP1A2, 2B6, and 3A4, based on assays performed in cryopreserved plateable human hepatocytes.

In the transporters assay, BL-8040 is not an inhibitor of organic anion-transporting polypeptide (OATP) 1B, organic anion transporter (OAT) 1, peptide transporter (PEPT) 1, and PEPT2. Inhibitions were < 25% for OATP1B3, OAT3, bile salt export pump, multi-drug resistance-1, and breast cancer resistance protein (14.6% to 22.8%) at concentrations up to 10 μM. BL-8040 inhibited multidrug and toxin extrusion protein (MATE) 1, MATE2-K, organic cation transporter (OCT)1, and OCT2 with apparent IC_{50} values of 2.7, 26.9, 20.1 and 5.1 μM, respectively. Considering BL-8040's protein binding profile in human plasma, the Cmax unbound (Cmax total x 1%) / IC_{50} of BL-8040 is less than the threshold (i.e., 0.1 for Food and Drug Administration [FDA] and 0.02 for European Medicines Agency [EMA]) considered to be indicative of potential inhibition in-vivo. The clinical inhibition potential for respective transporters is, therefore, considered to be remote based on FDA and EMA DDI guidance, respectively. In summary, the in-vitro DDI results suggest a low potential for DDIs with BL-8040.

8.1.2 Nonclinical Toxicology

The nonclinical toxicology program with BL-8040 consisted of a series of acute (single-dose) and multiple-dose (up to 28 days) toxicology studies, which were conducted in Sprague-Dawley rats and beagle dogs. SC and IV dose range-finding studies were subsequently followed by multiple-dose (up to 28 days) studies in each species. All definitive studies used the SC route, which is the clinical route of administration, appropriate dosing schedule and duration to adequately address the safety concerns for the indicated patient population and the intended clinical schedule (up to daily administrations for 4 weeks). In some studies, the IV route was used in order to maximize exposure. In the 14-day toxicology study, the highest tested dose in rats was 15 mg/kg and 9 mg/kg in the 7 days toxicology study in dogs. The definitive 28-day studies involved the daily administration of BL-8040 at doses of up to 6 mg/kg in rats and up to 3 mg/kg in dogs. These definitive multiple-dose studies included comprehensive clinical evaluations, systemic exposure evaluations (toxicokinetic) and the microscopic assessment of a complete panel of tissues. The multiple-dose dog studies included ECG measurements. Systemic exposure comparison between the non-clinical safety studies with the highest systemic exposures in humans suggested that the animal exposure levels of the high dose in the acute and repeat dose up to 7-day toxicology studies supported the human doses in the initial studies in patients (Study BKTSC001 and 201602037) and in healthy adults (BL-8040.02). However, in the subsequent repeat-dose toxicity studies (28 days), the exposure levels decreased and the systemic exposure comparison between the dose levels of no observed adverse effect level (NOAEL); 3 mg/kg in rat and 1 mg/kg in dog, to the highest systemic exposures reached in humans' clinical dose (single SC dose up to 1.25 mg/kg) indicates that there are no safety margins.

Exposures at doses determined as no observed effect level (NOEL) in safety pharmacology studies were slightly higher (central nervous system [CNS] and respiratory evaluations) or similar (cardiovascular effects mentioned above) to those observed in the initial clinical testing.

The safety pharmacology studies and general toxicology studies in rats and dogs identified the injection site, as well as the cardiovascular, respiratory and CNS systems as the potential target organs/tissues. The common findings included: transient anaphylactic-type reaction, CNS related clinical signs (ataxia and decreased activity in rats during first week of treatment/head twitching and decreased activity in dogs), increase in WBC counts (total and differential which correlated with the pharmacological activity of BL-8040), injection site lesions (SC hemorrhage and inflammation), respiratory effects (decrease in inspiration time, together with a marked increase in minute and tidal volumes) and cardiovascular effects (a dose-dependent short-lasting hypotensive effect followed by a dose dependent long-lasting hypertensive effect, combined with a dose dependent tachycardia seen in dogs). No histopathological adverse changes were identified in the pivotal toxicity studies excluding the injection sites. Similar local clinical symptoms were observed in rats and dogs immediately after first and subsequent BL-8040 administrations and consisted of transient anaphylactic-type reaction (edema and/or erythema of the face, ears, muzzle, and/or paws observed immediately). In dogs, the reactions were noticed from a few minutes up to approximately 2 hours following SC injection. Tolerability was demonstrated with repeated administrations over time as the magnitude of the systemic reactions was less pronounced with time and not

aggravated with increasing dose. Lesions at the injection sites (SC hemorrhage and inflammation) were associated with the high concentration formulation and/or volume of injection and/or repeated needle penetrations. In addition, the transient mild-to-moderate local AEs may be related to BL-8040 secondary PD action which leads to the localized activation of mast cells.

8.1.3 Nonclinical Safety Pharmacology

8.1.3.1 Cardiovascular System Assessment

The cardiovascular effects of BL-8040 were evaluated on arterial blood pressure, HR, and ECG after single SC administration of 0.23, 2.3 and 6.8 mg/kg to beagle dogs (3/sex). BL-8040 was tested in a crossover design after allowing a minimum washout period of 48 hours between treatments. Telemetric measurements started at least 3 hours before administration and were continued for 24 hours following dosing. Part 2 of the study included complementary investigations (6-lead ECG evaluation and animals' observation) was conducted following single SC administration of 6.8 mg/kg.

BL-8040 administered by the SC route to conscious telemetered dogs induced a dose-dependent hypotensive effect followed by a dose-dependent hypertensive effect at doses of 2.3 and 6.8 mg/kg (human equivalent dose [HED] of 1.28 mg/kg and 3.8 mg/kg, in respectively). BL-8040-induced hypotension was short lasting, approximately 30 minutes, whereas BL-8040-induced hypertension was more long-lasting, i.e., 10-12 hours at the dose of 6.8 mg/kg (3 folds higher than the clinical dose of 1.25 mg/kg). It is worthy of note that, arterial blood pressure changes were moderate in average at both doses of 2.3 and 6.8 mg/kg and were characterized by a high inter-individual variability.

These effects were combined with a dose-dependent tachycardia with a maximum effect observed from 30 minutes to 1 hour postdose, most likely reflex mediated. Thereafter, the duration of the tachycardia was well correlated with the hypertensive effect. The short lasting hypotension and reflex mediated tachycardia were associated with a high inter-individual variability, and were followed by a long term tachycardia and hypertension, that could be related to systemic and local reactions observed after dosing with BL-8040 at 2.3 and 6.8 mg/kg.

A shortening in PR and PQ intervals as well as in the QRS complex was found especially at the peak of tachycardia, suggesting that these electrocardiographic changes are likely a consequence of the tachycardic properties of BL-8040.

QT interval was also shortened in a dose-dependent manner at doses of 2.3 and 6.8 mg/kg. The QT interval shortening was well correlated with the tachycardic properties of BL-8040. Analysis of QTc interval changes using the probabilistic method or the QT shift method suggests that the QT interval shortening is related to a decrease in ventricular repolarization duration rather than a consequence of tachycardic properties of BL-8040.

No change in T wave morphology was observed in any of the groups. No arrhythmias attributable to BL-8040 administration were observed. No ECG changes (6 leads) attributable to the administration of BL-8040 at 6.8 mg/kg were observed.

Because few changes in HR only were found at the dose of 0.23 mg/kg, the NOAEL of BL-8040 on cardiovascular parameters in conscious dogs was considered at 0.23 mg/kg, when administered by the SC route. The HED was calculated to be 0.128 mg/kg.

In follow up evaluations the effect of BL-8040 on ECG parameters were assessed in the dose range finding (DRF) 7-day and in the 28-day repeat-dose studies in beagle dogs. In the DRF 7-day study, blood pressure and ECG measurements were performed at pre-treatment, and at 0.5 and 24 hours post treatment following BL-8040 treatment as single SC dose of up to 27 mg/kg (HED of 15 mg/kg) and 7 days repeat dose of up to 9 mg/kg (HED of 5 mg/kg). There were no clear effects of BL-8040 on the ECG parameters, blood pressure and HR values evaluated, as compared to pre-treatment data. Occasional increases in the HR at 30 minutes postdose or decrease in the systolic blood pressure were observed but due to low number of animals (1/sex) and inconsistencies between genders at various dose levels, the variations observed were attributed to a high inter-individual variability and could not be concluded. No significant changes were noted on the QT interval at any of the dose levels tested. In the 28 days, dogs were treated with BL-8040 dose levels of 0.3, 1, and 3 mg/kg (3/sex-main; 2/sex-recovery). The electrocardiography evaluations were performed on pre-treatment, Day 27 and Day 41 (recovery) prior to BL-8040 administration. No BL-8040-related differences were observed following repeated BL-8040 treatments up to 3 mg/kg (HED of 1.6 mg/kg) or recovery periods in the electrocardiography parameters evaluated as compare to the control group. In addition, no histopathological adverse findings were identified in the cardiovascular system tissues.

8.1.4 Clinical Data

As of April 2021, three clinical trials were completed, one was closed due to lack of recruitment, one is in the stages of closure, seven clinical trials are ongoing, and three are in long-term follow-up. The trials are conducted either as BioLineRx sponsored studies, Sponsor-Investigator trials, or as studies sponsored by collaborative partners of BioLineRx. Details are provided below.

Completed studies:

- Study BKTSC001 was a non-randomized, open-label, single administration, dose-escalation study, where BL-8040 was administered to patients with newly diagnosed multiple myeloma who were undergoing treatment with chemo-mobilization and granulocyte-colony stimulating factor (G-CSF).

- Study BL-8040.02 was a Phase I clinical study in healthy subjects evaluating BL-8040 as a single agent for stem cell mobilization.

- Study BL-8040.01 is a Phase IIa clinical trial for the treatment of adult relapsed/refractory AML patients with a combination of BL-8040 and cytarabine (Ara-C).

Closed studies:

- Study BL-8040.AML.202, 'BATTLE', was a Phase Ib/II study evaluating safety, tolerability and efficacy of the BL-8040 and atezolizumab combination for maintenance treatment in patients with AML. One subject was treated. In April 2020, the study was terminated due to lack of recruitment.

Studies in closure stages:

- Study BL-8040.06, a Phase Ib study evaluating the efficacy and safety of BL-8040 followed by standard immunosuppressive therapy in adult subjects with aplastic anemia or hypoplastic myelodysplastic syndrome.

Studies in long-term follow-up:

- Study 201602037, an investigator-sponsored Phase II study evaluating the safety and efficacy of BL-8040 for the mobilization of donor HSC and allogenic transplantation in patients with advanced hematological malignancies.

- Study 2016-0410, an investigator-initiated Phase IIb pilot study to assess the efficacy, safety and PD effects of pembrolizumab and BL-8040 in patients with metastatic pancreatic cancer.

- Study WO39608, a Roche-sponsored study to evaluate the combination of atezolizumab and BL-8040 in patients with metastatic pancreatic cancer.

Ongoing studies:

- Study BL-8040.SCM.301, called "GENESIS", is a Phase III study evaluating safety, tolerability and efficacy of combination treatment of BL-8040 and G-CSF as compared to placebo and G-CSF for the mobilization of HSCs for autologous transplantation in subjects with multiple myeloma.

- Study BL-8040.PAC.201, "COMBAT", a Phase II clinical trial assessing the safety and efficacy of the combination of BL-8040 and pembrolizumab for metastatic pancreatic cancer.

- Investigator-sponsored study UKH062014, termed "BLAST", a Phase II study conducted in Germany. This study is assessing the efficacy of BL-8040 as an add-on therapy to standard of care consolidation therapy in AML patients in first complete remission. The study is a double blind, randomized placebo-controlled study.

- Investigator-sponsored study 201606146, a Phase IIa Study of BL-8040 in combination with nelarabine for relapsed or refractory T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma.

- Investigator-sponsored study Chemo4METPANC, a Phase II study with combination chemotherapy (gemcitabine and Nab-Paclitaxel), chemokine (C-X-C) motif receptor

4 inhibitor (BL-8040), and immune checkpoint blockade (cemiplimab) in metastatic treatment naïve pancreas adenocarcinoma.

- Investigator-sponsored COVID study: A Phase Ib, open-label study designed to evaluate the safety of BL-8040 (a CXCR4 antagonist) in patients with Acute Respiratory Distress Syndrome secondary to COVID-19 and other respiratory viral infections.

- Collaborative study YO39609, termed "Morpheus-Gastric Cancer", a Phase Ib/II studies sponsored by Roche to evaluate immunotherapy-based treatment combinations in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer.

8.1.5 Pharmacokinetics in Humans

Study BL-8040.02 was a healthy subject study conducted in two parts. In Part 1, subjects received two injections of BL-8040 (once daily on 2 consecutive days) of 0.5 mg/kg (Cohort 1), 0.75 mg/kg (Cohort 2), and 1 mg/kg (Cohort 3). Each cohort consisted of 6 subjects receiving BL-8040 and 2 subjects receiving matching placebo, in a double-blinded manner. Based on the safety and PD data from Part 1, the single dose of 1 mg/kg was selected for Part 2 of the study. Part 2 used an open-label design in which each subject received a single BL-8040 injection of 1 mg/kg BL-8040, followed by a standard leukapheresis procedure starting approximately 4 hours after the BL-8040 injection.

After SC administration of BL-8040 on Day 1, the appearance of the compound in plasma was rapid, with a median Tmax ranging between 0.25 and 0.5 hour. Thereafter, plasma concentrations declined mono-exponentially with a short t½ of approximately 1 hour. For that reason, plasma levels of BL-8040 were below the limit of detection in the majority of subjects by 8 hours and in all subjects at 23 hours after dosing. Increases in the dose of BL-8040 led to overall approximate proportional increases in plasma exposure, as measured by Cmax, AUC0-t, AUC0-24, and AUC0-inf. Dose-normalized Cmax and AUC0-24 and t½ values were comparable across the 3 dose groups suggesting dose proportionality across the 0.5 to 1.0 mg/kg dose range.

In Study 201602037, a single SC dose of 1 mg/kg or 1.25 mg/kg BL-8040 was administered to healthy donors. Hematopoietic cells were collected for transplantation in sibling recipients. The PK parameters of BL-8040 in the donors show rapid appearance in plasma and short t½. By 24 hours, plasma levels of BL-8040 were below the limit of quantitation in 18 of the 25 subjects.

Study BL-8040.01 was a Phase IIa, 2-part study to assess the safety and efficacy of BL-8040 (0.5-2.0 mg/kg) in combination with high dose cytarabine (Ara-C) in patients with relapsed/refractory AML (r/rAML). Part 1 was a dose escalation phase (3+3 dosing) and Part 2 was a dose expansion phase. Subjects received SC injections over 2 days (one per day) as monotherapy followed by concurrent daily administration of BL-8040 with Ara-C standard salvage chemotherapy over 5 days. During the "combined period," BL-8040 was administered 4 hours prior to chemotherapy.

A summary of PK parameters on Day 1 (Table 1) and Day 7 (Table 2) is provided. Mean predose BL-8040 concentrations are provided by day in Table 3. BL-8040 was rapidly absorbed after SC administration, reaching maximum concentrations between 0.25 to 1 hour after dosing on Day 1, and declining with a half-life of 1 to 3 hours on average. After repeated daily administration, the PK of BL-8040 on Day 7 were comparable to Day 1. BL-8040 did not accumulate to any significant extent after daily dosing and predose levels were consistent across 6 measurements. Increases in the dose of BL-8040 led to increases in systemic exposure. The PK characteristics of BL-8040 in r/r AML patients are similar to those observed in healthy subjects.

Table 1: Summary of Day 1 BL-8040 Pharmacokinetic Parameters after Subcutaneous Administration in Subjects with Relapsed/Refractory Acute Myeloid Leukemia (Study BL-8040.01)

Dose (mg/kg)		t½ (h)	Tmax (h)	Cmax (ng/mL)	AUC0-t (h*ng/mL)	AUC0-24 (h*ng/mL)	AUC-inf AUC0-t	Cmax/D (kg*ng/mL/mg)	AUC-inf/D (h*kg*ng/mL/mg)
0.5	n	1	3	3	3	1	1	3	1
	Mean	1.23	0.833	380	661	671	671	760	1340
	SD	NR	0.289	33.6	55.3	NR	NR	67.2	NR
	Min	NR	0.500	348	605	NR	NR	696	NR
	Median	NR	1.00	377	662	NR	NR	754	NR
	Max	NR	1.00	415	716	NR	NR	830	NR
	CV%	NR	34.6	8.84	8.36	NR	NR	8.84	NR
0.75	n	3	3	3	3	3	3	3	3
	Mean	1.50	0.417	376	792	809	810	501	1080
	SD	0.484	0.144	155	447	439	438	207	584
	Min	1.06	0.250	200	279	305	307	267	410
	Median	1.41	0.500	434	998	1020	1020	579	1350
	Max	2.02	0.500	494	1100	1110	1110	659	1480
	CV%	32.4	34.6	41.3	56.4	54.2	54.0	41.3	54.0
1.0	n	5	6	6	6	5	5	6	5
	Mean	1.40	0.792	712	1390	1550	1550	712	1550
	SD	0.336	0.332	277	541	484	484	277	484
	Min	1.07	0.250	336	707	933	933	336	933
	Median	1.38	1.00	750	1370	1500	1500	750	1500
	Max	1.93	1.00	1010	2080	2130	2130	1010	2130
	CV%	24.0	42.0	38.9	38.9	31.2	31.2	38.9	31.2

Dose (mg/kg)		t½ (h)	Tmax (h)	Cmax (ng/mL)	AUC0-t (h*ng/mL)	AUC0-24 (h*ng/mL)	AUC-inf AUC0-t	Cmax/D (kg*ng/mL/mg)	AUC-inf/D (h*kg*ng/mL/mg)
1.25	n	4	4	4	4	4	4	4	4
	Mean	2.06	0.875	1670	3020	3060	3070	1340	2450
	SD	1.92	0.250	522	1340	1340	1350	418	1080
	Min	0.660	0.500	1290	1570	1600	1600	1030	1280
	Median	1.34	1.00	1480	2880	2940	2940	1180	2350
	Max	4.89	1.00	2430	4750	4750	4790	1940	3830
	CV%	93.3	28.6	31.3	44.4	43.7	44.2	31.3	44.2
1.5	n	18	19	19	19	18	18	19	18
	Mean	2.11	0.618	1940	3650	3840	3860	1290	2570
	SD	1.57	0.281	803	1640	1520	1530	535	1020
	Min	0.525	0.250	533	571	575	575	355	384
	Median	1.34	0.500	1910	3580	3650	3670	1270	2450
	Max	5.18	1.00	3420	6670	6700	6700	2280	4470
	CV%	74.1	45.4	41.4	44.9	39.6	39.6	41.4	39.6
2.0	n	3	3	3	3	3	3	3	3
	Mean	2.67	1.00	4020	8340	8370	8390	2010	4200
	SD	1.27	0.00	1510	2290	2260	2260	753	1130
	Min	1.29	1.00	2630	6520	6610	6610	1320	3300
	Median	2.93	1.00	3810	7590	7590	7630	1910	3810
	Max	3.79	1.00	5620	10900	10900	10900	2810	5470
	CV%	47.7	0.00	37.5	27.5	27.0	27.0	37.5	27.0

Note: NR = not reported (n <3)

Table 2: Summary of Day 7 BL-8040 Pharmacokinetic Parameters after Subcutaneous Administration in Subjects with Relapsed/Refractory Acute Myeloid Leukemia (Study BL-8040.01)

Dose (mg/kg)		t½ (h)	Tmax (h)	Cmax (ng/mL)	AUC0-t (h*ng/mL)	AUC0-24 (h*ng/mL)	Cmax/D (kg*ng/mL/mg)	AUC-inf/D (h*kg*ng/mL/mg)
0.5	n	3	3	3	3	3	3	3
	Mean	1.52	0.500	546	621	634	1090	1270
	SD	1.15	0.00	498	373	364	996	727
	Min	0.556	0.500	65.3	192	216	131	432
	Median	1.21	0.500	513	806	815	1030	1630
	Max	2.79	0.500	1060	866	872	2120	1740
	CV%	75.5	0.00	91.2	60.1	57.3	91.2	57.3
0.75	n	1	3	3	3	1	3	1
	Mean	1.29	1.17	365	716	1100	487	1460
	SD	NR	0.764	205	340	NR	273	0.00
	Min	NR	0.500	224	403	NR	299	1460
	Median	NR	1.00	271	666	NR	361	1460
	Max	NR	2.00	600	1080	NR	800	1460
	CV%	NR	65.5	56.1	47.6	NR	56.1	0.00
1.0	n	5	6	6	6	5	6	5
	Mean	1.50	0.708	799	1520	1810	799	1810
	SD	0.417	0.332	451	795	584	451	584
	Min	1.15	0.250	167	289	1280	167	1280
	Median	1.44	0.750	767	1500	1660	767	1660
	Max	2.20	1.00	1540	2700	2740	1540	2740
	CV%	27.9	46.9	56.4	52.2	32.3	56.4	32.3

Dose (mg/kg)		t½ (h)	Tmax (h)	Cmax (ng/mL)	AUC0-t (h*ng/mL)	AUC0-24 (h*ng/mL)	Cmax/D (kg*ng/mL/mg)	AUC-inf/D (h*kg*ng/mL/mg)
1.25	n	4	4	4	4	4	4	4
	Mean	4.71	1.00	1510	3430	3430	1210	2750
	SD	1.27	0.707	480	352	352	384	282
	Min	3.50	0.500	913	3080	3080	730	2470
	Median	4.43	0.750	1590	3380	3380	1270	2710
	Max	6.49	2.00	1960	3880	3880	1570	3100
	CV%	27.0	70.7	31.7	10.3	10.3	31.7	10.3
1.5	n	18	19	19	19	19	19	19
	Mean	4.12	0.671	1400	3420	3440	935	2290
	SD	1.64	0.264	706	1850	1840	470	1220
	Min	1.24	0.250	472	1040	1090	315	728
	Median	4.41	0.500	1360	3020	3250	907	2160
	Max	6.72	1.00	2870	6970	6970	1910	4650
	CV%	39.9	39.4	50.3	54.0	53.4	50.3	53.4
2.0	n	3	3	3	3	3	3	3
	Mean	5.48	1.33	2490	8880	8880	1250	4440
	SD	3.03	0.577	1040	2160	2160	520	1080
	Min	3.59	1.00	1330	6610	6610	665	3300
	Median	3.88	1.00	2820	9130	9130	1410	4570
	Max	8.98	2.00	3330	10900	10900	1670	5450
	CV%	55.3	43.3	41.7	24.3	24.3	41.7	24.3

Note: NR = not reported (n <3)

Table 3: Mean (SD) Predose BL-8040 Concentrations (ng/mL) by Day (Study BL-8040.01)

Dose (mg/kg)	Day					
	2	3	4	5	7	8
0.5 (n = 3)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
0.75 (n = 3)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1.0 (n = 6)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.83 (2.84)	0.00 (0.00)
1.25 (n = 4)	1.56 (3.11)	1.94 (3.35)	9.02 (NR)	6.06 (4.06)	7.59 (2.56)	8.50 (1.37)
1.5 (n = 19)	1.67 (2.85)	3.65 (3.91)	3.01 (3.97)	6.84 (8.30)	8.35 (7.37)	7.00 (5.15)
2.0 (n = 3)	4.00 (3.58)	11.7 (8.25)	14.7 (10.1)	25.6 (18.6)	39.6 (42.1)	36.3 (37.3)

Note: NR = not reported (n <3). Day 8 is the 24-hour sample of Day 7
Ara-C was administered on Days 3-7

8.1.6 Safety Data in Human

A total of 86 subjects were treated with BL-8040 in three completed BL-8040 clinical studies (BKTSC001, BL-8040.01, and BL-8040.02). Among the BL-8040-treated subjects, 1238 AEs were reported, of which 787 events reported for 71 subjects (82.6%), and are considered related to BL-8040.

In completed clinical studies with BL-8040 the following adverse reactions were observed with the highest frequencies (n=86 subjects): injection site reactions including: pain (59.3% of subjects), erythema (43%), oedema (29.1%), pruritus (23.3%), and rash (11.6%); and systemic reactions: flushing (32.6%), pruritus (not at the injection site; 32.6%), hot flushes (27.9%) and urticaria (23.3%). These two groups of reactions are well managed with pre-medication and/or post event treatment using antihistamines and/or steroids. Additional related AEs reported with relatively high frequency include nausea (20.9%), vomiting (12.8%), asthenia/fatigue (17.5%), paraesthesia (12.8%) and dizziness (1.6%).

Additional uncommon treatment related adverse effects reported in ongoing clinical studies include hypokalemia, thrombocytopenia, hyperleukocytosis, elevated liver function tests, diarrhea, anaphylaxis, injection site skin necrosis (2 reported cases), abdominal pain, chest pain, bradycardia, and severe allergic reactions/anaphylaxis.

The majority of the adverse reactions observed were transient and mild to moderate.

Of note, leukocytosis is an expected PD effect of treatment with BL-8040. Although none of the BL-8040-treated subjects in the completed studies experienced leukostasis (BKTSC001 in multiple myeloma patients, BL-8040 in healthy subjects and BL-8040.01 in adult r/r AML), leukostasis is a perceived potential safety issue based on the BL-8040 mechanism of action, and certain patient populations may be at higher risk.

Uncommon adverse reactions include one serious adverse reaction of acute leukocytosis accompanied by acute respiratory distress and encephalopathy and two serious adverse reactions of anaphylaxis. Other adverse reactions reported to date include paraesthesia, musculoskeletal pain, headache, constipation, diarrhea, abdominal pain, fatigue, nausea, vomiting, hypotension, increased liver transaminases, increased alkaline phosphatase, dyspnea and hypokalemia.

8.1.7 Human Cardiac Safety

Formal cardiac safety evaluation has not been performed to date for BL-8040. Few cardiac AEs and no serious ECG AEs have been reported to date.

8.2 Moxifloxacin

Moxifloxacin hydrochloride is a synthetic C-8-methoxy-fluoroquinolone antimicrobial agent. It has different properties than other quinolone agents. While still active against gram negative pathogens, it is also highly active against gram-positive cocci, aerobic, anaerobic, intracellular bacteria and "atypical" organisms such as Mycoplasma and Chlamydia. Hence, it is effective for the treatment of respiratory tract infections, including acute exacerbations of chronic bronchitis, community-acquired pneumonia, and acute bacterial sinusitis. It is also indicated for the treatment of complicated and uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. The recommended oral dose is 400 mg once daily for 5 - 21 days, depending on the specific infection (Avelox 2019).

Moxifloxacin is a reversible blocker of the potassium current of the cardiac rapid delayed rectifier (*I*Kr) channel and causes a mean increase of the QTc interval of 10–14 msec between 2 and 4 hours after a single oral dose of 400 mg (Taubel et al, 2014, Florian et al, 2011, Alexandrou et al, 2006). Based on moxifloxacin effect on QT interval duration, it has been used standardly as a positive control in most thorough-QT (TQT) studies to determine study sensitivity.

Following administration of the usual therapeutic dose (400 mg) under fasting conditions, Cmax occurs at approximately 1.5 hours and the t½ of moxifloxacin is approximately 13 hours. Moxifloxacin can be given concurrently with food, but not with antacids containing magnesium or aluminum or preparations containing sucralfate or metal cations, such as iron or zinc. Coadministration with a high fat meal (i.e., 500 calories from fat) does not affect the overall absorption and systemic exposure to moxifloxacin, but increases the time to maximum blood concentration (to approximately 2.5 hours) and decreases the maximum blood concentration (Avelox 2019).

Moxifloxacin prolongs QT interval duration and is used as a positive control in most TQT studies to determine study sensitivity.

The most common AEs seen with moxifloxacin are nausea, diarrhea, headache, and dizziness. Moxifloxacin is in the FDA pregnancy category C.

8.3 Rationale

8.3.1 Rationale for this Study and Study Design

Regulatory guidance (ICH E14 2005) has emphasized the need to obtain clear robust data on the effect of new chemical entities on ECG parameters with focus on cardiac repolarization as measured by the QTc duration. Though many Phase I, II, and III trials may be conducted, they usually have 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 performed in healthy subjects to eliminate variables known to have an effect on ECG parameters (e.g., concomitant drugs, diseases). A supratherapeutic dose of BL-8040 is required to mimic the exposure in healthy subjects that may occur in the target patient population under the worst of circumstances (e.g., intrinsic or extrinsic factors such as DDIs, impaired hepatic or renal function, 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.

The random order design of treatment sequence used the following 12-sequence scheme, with subjects randomly assigned to a sequence, as shown in Table 4. This schedule allows for blinding of all but the moxifloxacin treatment sequence, and does not require equal numbers of subjects in each sequence.

The washout period between dosing in each period is considered sufficient to prevent carryover effects of the preceding treatment.

8.3.2 Rationale for the Dose Selection

As a peptide, and based on nonclinical and clinical data, BL-8040 exposure is not expected to be significantly increased by the intrinsic or extrinsic factors which may alter the exposure of small molecules (meal status, DDIs, hepatic insufficiency, or renal insufficiency). BL-8040 and metabolic breakdown products are also not expected to accumulate with repeated dosing.

In the absence of significant accumulation with repeated dosing or the need to slowly up-titrate the dose of a new drug, a crossover study design is preferred for a dedicated QT trial, as subjects act as their own controls. The dosage of BL-8040 used clinically is expected to be 1.25 mg/kg administered SC once daily, as a single dose or repeated dosing depending on the indication. There does not appear to be significant accumulation of BL-8040 following repeated administration for up to 7 days (Section 8.1.5). Therefore, a single-dose, crossover design is appropriate. The clinical/therapeutic dose of BL-8040 to be administered in this trial will therefore be 1.25 mg/kg as a single SC dose.

The maximum tolerated dose of BL-8040 has not been established. Based on the results of healthy subject and patient studies, a 1.25 mg/kg SC dose has been well tolerated and results in a median Cmax of approximately 1600 ng/mL. BL-8040 is rapidly metabolized, and DDIs are not anticipated to result in elevated BL-8040 exposures. The highest clinically relevant

exposure is anticipated to be approximately a 1.5 fold multiple of the exposure following administration of the therapeutic dose. Doses of up to 2 mg/kg for 7 consecutive days have been administered to patients with good tolerability (Study BL-8040.01). A single 2 mg/kg SC dose, 1.6 times the anticipated clinical dose of 1.25 mg/kg, will therefore be utilized as the supratherapeutic dose. The supratherapeutic dose is anticipated to yield a Cmax of 2600-5600 ng/mL, which is anticipated to be 1.6 to 3.5-fold higher than the Cmax which will be achieved with the clinical dose. It is anticipated that this supratherapeutic exposure will adequately cover the highest clinically relevant exposure for BL-8040. Based on the data from the single ascending dose study, there is not expected to be significant accumulation of BL-8040, nevertheless, a washout will be included between treatment periods.

An oral 400 mg moxifloxacin will be used as a positive control (Florian et al, 2011) to determine the "assay sensitivity" of this study with an expected magnitude change from baseline placebo-corrected of 5-10 msec using a time-averaged analysis or 10-15 msec using a time-matched analysis. Moxifloxacin has been shown, in crossover design studies, to produce peak prolongation for ΔΔQTc ranging from 10 to 15 msec. The current study was designed to detect an increase of 5 msec in the QTc threshold of regulatory concern, i.e., lower bound of a one-sided 95% CI > 5 msec (Avelox 2019, Stass et al, 1998; Taubel et al, 2014).

8.3.3 Rationale for Premedication Selection

Based on experience in clinical studies to date, the most common adverse reactions observed following BL-8040 treatment include local injection site reactions including pain, erythema, oedema, pruritus and systemic reactions flushing, generalized pruritus, hot flushes, and urticaria. Two serious adverse reactions of anaphylaxis have occurred following BL-8040 treatment. Premedication with antihistamines including cetirizine (H1 blocker) and nizatidine (H2 blocker), as well as and montelukast (leukotriene antagonist) is recommended in order to prevent or minimize these reactions. Furthermore, an analgesic (acetaminophen) is recommended to reduce the injection site pain.

The timing of premedication administration in all BL-8040 clinical studies is 1 hour prior to study drug administration to allow for onset of pharmacological activity of premedication. Based on this, premedication will be administered 1 hour (± 15 minutes) prior to study drug administration and prior to the first cardiodynamic ECG baseline measurement scheduled at -0.75 hours predose.

8.4 Risks and/or Benefits to Subjects

The therapeutic (1.25 mg/kg) and supratherapeutic (2 mg/kg) doses of BL-8040 administered in this study are not anticipated to induce any potential risk or benefit to subjects participating in this study. The exposure levels are expected to be tolerable for the subjects and without any major safety concern. Expected AEs are reported in the IB (IB v8.0, 2020).

The moxifloxacin dosing regimen for this study is within the FDA-approved dosing regimen. It has been marketed in the US since 1999 as Avelox® and continues to be marketed in the

generic form. The risk of moxifloxacin-induced Torsade de Pointes is expected to be minimal when a single dose of the drug is administered at the recommended dose (Avelox 2019).

The safety monitoring practices employed by this protocol (i.e., AEs, 12-lead safety ECG, vital sign measurements, clinical laboratory tests, and physical examination) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

Premedication (as detailed in Section 12.1) will be administered to all subjects prior to dosing in each period as to minimize the risk of injection-related reactions.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at Screening and during the study.

9 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the QTc effects (ECG) of BL-8040 1.25 mg/kg (therapeutic dose) and 2 mg/kg (supratherapeutic dose) following a single SC injection relative to placebo in healthy subjects.	• Evaluation of the relationship between the plasma concentration of BL-8040 and ΔΔQTcI (placebo adjustment for ΔQTcI will be performed in the concentration-QTc model).
Secondary	
• To evaluate the safety, tolerability, and PK of single therapeutic and supratherapeutic SC injections of BL-8040 in healthy subjects.	• AEs, 12-lead safety ECGs, vital signs, clinical laboratory tests, and physical examinations. • AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL/F, and Vz/F for BL-8040, as appropriate.
• To assess the effects of single therapeutic and supratherapeutic SC injections of BL-8040 on non-QT interval ECG parameters (HR, RR, PR, and QRS intervals) in healthy subjects.	• Time-point change from baseline, placebo-adjusted in ΔΔQTcI • Time-point change from baseline, placebo-adjusted, for HR, RR, QTcF, PR, and QRS • Categorical outliers for HR, RR, PR, QRS, QTcI, and QTcF • Frequency of treatment-emergent changes in ECG morphology
• To evaluate assay sensitivity (i.e., to evaluate the effect of a positive control, a single oral 400 mg dose of moxifloxacin, on the QTc interval in healthy subjects).	• Evaluation of the relationship between the plasma concentration of moxifloxacin and ΔQTcI in order to demonstrate assay sensitivity.
Exploratory	
• To evaluate the PD effects of single therapeutic and supratherapeutic SC injections of BL-8040.	• PD evaluations will include CD34+ and receptor occupancy (RO).

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a randomized, double-blind (in respect to BL-8040 and BL-8040-matching placebo dosing), placebo- and positive-controlled, 4-period, 4-way crossover study.

Approximately 40 healthy, adult male and female subjects will be enrolled to ensure at least 26 subjects complete the study. Every attempt will be made to enroll no less than 30% of either gender.

Screening activities will occur within 28 days prior to check-in (Day -2 in Period 1).

Subjects who are found to be eligible following screening procedures will be invited and admitted to the CRU on Day -2 of Period 1 and will remain at the CRU until the end of Period 4 (Section 10.1.1).

A continuous 12-lead cardiodynamic ECG recording will be collected for approximately 24 hours on Day -1 of Period 1 for use in the optimized QTcI baseline calculations.

On Day 1 of Period 1, subjects will be randomized to 1 of 12 treatment sequences (Table 4). Each treatment sequence comprises 4 treatment periods.

On Day 1 of each period, subjects will receive single-dose SC injection of BL-8040 (therapeutic or supratherapeutic dose), single-dose SC injection of BL-8040-matching placebo, or a single oral dose of moxifloxacin. Cardiodynamic readings, plasma PK samples, and blood PD samples will be collected at different time points prior to dosing and up to 24 hours postdose in each period, as appropriate.

There will be a washout period of 5-7 days between dosing in each period.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations (e.g., AEs, 12-lead safety ECG, vital sign measurements, clinical laboratory tests, and physical examination).

Early discontinued subjects will not be replaced.

10.1.1 Confinement and Follow-Up

Subjects will be housed in the CRU on Day -2 of Period 1, at the time indicated by the CRU, until after completion of study procedures on Day 2 of Period 4.

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

All subjects who received at least one dose of any study drug (including subjects who terminate the study early) will return to the CRU 7 ± 2 days after the last dose for follow-up

procedures, and to determine if any AE has occurred since the last study visit. A review of AEs and concomitant medication will also be performed at this follow-up visit.

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure (i.e., 7 ± 2 days after the last dose of study drug) as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

11.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, males and females between the ages of 18 and 55 years, inclusive, at Screening.

2. Body weight between 50-109 kg (inclusive) and body mass index (BMI) within 18.0-29.99 kg/m^2 (inclusive) at Screening.

3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI or designee.

4. Current non-smokers who have not used any nicotine-containing products (chewed or smoked) or replacement products including electronic cigarettes for at least 3 months prior to first dosing.

5. Women must meet one of the following criteria: a) postmenopausal; b) surgically sterile; c) of childbearing potential and practicing contraception, as described below:
   - Postmenopausal (postmenopausal women must have no menstrual bleeding for at least 1 year prior to first dosing and menopause is confirmed by FSH levels consistent with postmenopausal status), or
   - Surgically sterile (e.g., hysterectomy, bilateral oophorectomy, hysteroscopic sterilization) for at least 6 months prior to first dosing, or
   - Women of childbearing potential must be non-lactating and agree to either using a highly effective acceptable form of birth control (e.g., non-hormonal intrauterine device plus condom and spermicide).

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male.)

7. If male, must agree not to donate sperm from the first dosing until 90 days after the last dosing.

8. Understands the study procedures in the informed consent form (ICF), and is willing and able to comply with the protocol.

11.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Past or present diseases, which, as judged by the PI or designee, may affect the outcome of this study or pose an additional risk to the subject by their participation in the study, including, but not limited to, significant medical abnormality including: psychiatric, neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, metabolic, endocrinologic, or autoimmune disorder.

2. Is mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.

3. Positive result for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody at Screening.

4. Family history of QTc prolongation or of unexplainable sudden death at <50 years of age.

5. History or presence of any of the following:
   - sick sinus syndrome, second or third degree atrioventricular block, myocardial infarction, pulmonary congestion, symptomatic or significant cardiac arrhythmia, prolonged QTcF interval, or conduction abnormalities;
   - ischemic heart disease, symptomatic arrhythmias, or poorly controlled hypertension.

6. Knowledge of any kind of cardiovascular disorder/condition known to increase the possibility of QT prolongation or history of additional risk factors for torsade de pointes (e.g., heart failure, clinically significant hypokalemia, family history of Long QT Syndrome or Brugada Syndrome) or cardiac conduction disorders.

7. Any condition that may interfere with the absorption, metabolism, or elimination of the study drug.

8. History of, or active, alcohol or illicit drug abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, manual, within 2 years prior to the first dosing. Alcohol abuse is defined as an average intake of two or more drinks (12 oz beer, 1.5 oz of hard liquor, or equivalent) per day.

9. Laboratory safety test results that are outside of the normal reference ranges (unless clinically acceptable to the PI or designee) at Screening.

10. Resting supine HR <50 bpm or >100 bpm at Screening or check-in (Day -2). Minor deviations will be acceptable if considered to be of no clinical significance by the PI or designee.

11. Resting supine systolic blood pressure <90 mmHg or >140 mmHg; resting supine diastolic blood pressure <50 mmHg or >90 mmHg at Screening or check-in.

12. Significant history or presence of ECG findings at Screening or check-in (Day -2), including:
    - QTcF >450 msec
    - QRS >110 msec, if >110 msec, result will be confirmed by a manual over read
    - PR >200 msec
    - Second or third-degree atrioventricular (AV) block.
13. Significant history or presence of ECG findings as judged by the PI or designee at Screening or check-in (Day -2), including:
    - ECG abnormalities which interfere with accurate QT measurement
    - T wave flattening or other abnormalities which in the opinion of the PI (or designee) may interfere with the analysis of QT intervals
    - Any rhythm other than sinus rhythm, which is interpreted by the PI (or designee) to be clinically significant.
14. Significant safety laboratory abnormalities that would place the subject at undue risk in the PI or designee's opinion, including but not limited to serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) >1.2 x upper limit of normal at Screening or check-in.
15. Positive urine cotinine at Screening.
16. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days or 5 half-lives (whichever is longer) prior to the first dosing or likelihood that such treatment will be needed at any time during the study (unless approved in advance by the Sponsor). Medications listed in Section 11.4.2 will be allowed.
17. Participation in another clinical study within 30 days prior to the first dosing. The 30-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 Period 1 of the current study.
18. Donation of blood or blood loss >500 mL within the 56 days prior to the first dosing.
19. Plasma donation within 7 days prior to the first dosing.
20. Any condition or situation that, in the opinion of the PI or designee, would prevent proper evaluation of the safety, PK, and/or PD of the study drug according to the study protocol (e.g., poorly compliant subject, poor venous access, allergies to medical plastics/latex/adhesive dressing/medical tape).
21. History of hypersensitivity or allergy to moxifloxacin or any study medication.

22. History of tendonitis or tendon rupture with moxifloxacin or any other quinolone type drug.

23. History of unexplained loss of consciousness, unexplained syncope, near drowning with hospital admission.

24. Use of any marijuana product within 6 months prior to the first dosing.

25. Use of illicit drugs or tetrahydrocannabinol-containing medicines within 6 months prior to the first dosing.

26. Female subjects with a positive pregnancy test at Screening or check-in or lactating.

27. Positive urine drug or alcohol results at Screening or check-in.

28. Has tattoo(s) or scarring at or near the site of injection or any other condition which may interfere with injection site examination, in the opinion of the PI or designee.

29. Subjects intending to lose weight during the study.

11.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

Subjects' participation in the study maybe discontinued due to the following reasons:

- Subjects withdrew consent.
- Request of the Sponsor.
- Request of the PI or primary care physician.
- Non-adherence to study requirements, e.g., difficulties on blood collection.
- Protocol violation.
- AEs.
- Death.
- Pregnancy.
- QTcF interval > 500 msec, confirmed on recheck within 5 minutes, on any scheduled safety ECG or at any time an unscheduled ECG for safety was deemed necessary by the PI, or an increase > 60 msec from baseline.
- Lost to follow-up.

If a subject is withdrawn from the study due to any of the reasons above, every effort should be made to determine the reason and all procedures for early termination should be performed.

11.4 Study Restrictions

11.4.1 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 24 hours prior to the first dose and until collection of the last PK sample;
- Alcohol: 72 hours prior to the first dose and until collection of the last PK sample;
- Grapefruit/Seville orange: 7 days prior to the first dose and until collection of the last PK sample.

11.4.2 Concomitant Medication

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2.

Premedication as described in Section 12.1 will be allowed.

Treatment of AEs may include the following medication: hydrocortisone (100 mg IV), other steroids (oral, topical, or IV), anti-histamines, and/or analgesics (e.g., acetaminophen up to 2 g per 24 hours, ibuprofen up to 1.2 g per 24 hours) may be administered at the discretion of the PI or designee to treat systemic reactions and injection site reactions (Section 12.7). Negative chronotropic drugs, such as beta blockers, should be avoided as rescue medication.

If deviations occur, the PI or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

11.4.3 Meals

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each oral dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

In each period, subjects will fast overnight for at least 10 hours prior to each dosing and will continue the fast for at least 4 hours postdose.

On Day -1 of Period 1, subjects will follow a similar time matched (± 5 minutes) fasting and meal schedule as planned for Day 1 of Period 1 according to the anticipated time of dosing on Day 1 of Period 1.

When scheduled at the same time, meals and snacks will be provided following completion of the cardiodynamic reading and must be scheduled to be completed at least 60 minutes

before any scheduled ECG time point (i.e., standard 12-lead safety ECG or cardiodynamic ECG). Subjects are not required to consume meals or snacks in their entirety.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each period.

11.4.4 Activity

Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECG recording on Day -1 of Period 1 and Day 1 of each period. On Day 1 of each period, subjects will remain awake until after data collection at the 16-hour time point, as the QT-RR relationship is different during sleep. Subjects must also be awakened at least 1 hour prior to the cardiodynamic ECG recording at the 24-hour time point in each period.

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures. After the first 4 hours postdose, subjects will remain ambulatory, seated upright, or semi-reclined and awake, except when a supine position is dictated by study procedures, until the 16-hour postdose cardiodynamic ECG recording. Subjects must rest in the supine position for at least 10 minutes prior to each ECG extraction window and throughout the duration of the ECG extraction window with minimal movement and minimal exposure to noise and other environmental stimuli.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

12 TREATMENTS

12.1 Premedication Administered

Nizatidine 15 mg/mL oral solution, cetirizine hydrochloride 10 mg tablets, acetaminophen 500 mg tablets, and montelukast sodium 10 mg tablets will be provided.

In each period, the following medications will be administered 1 hour (± 15 minutes) prior to study drug administration and prior to the first baseline cardiodynamic ECG measurement scheduled at the -0.75 hour time point:

- 300 mg nizatidine (H2 blocker), single oral dose
- 10 mg cetirizine (H1 blocker), single oral dose
- 1 g acetaminophen (analgesic), single oral dose
- 10 mg montelukast (mast cell stabilizer), single oral dose

The time of premedication administration is to be recorded on site documentation and in the case report form (CRF).

12.2 Treatments Administered

Both BL-8040 and BL-8040-matching placebo will be provided as lyophilized powder for reconstitution with 2 mL sterile 0.45% sodium chloride (half saline) prior to SC injection. BL-8040 drug product is formulated as a sterile and non-pyrogenic lyophilized powder in a vial containing 73 mg BL-8040 free base peptide (on dry basis) and 26 mg of mannitol. BL-8040-matching placebo is formulated as a sterile and non-pyrogenic lyophilized powder in a vial containing 50 mg of mannitol.

BL-8040 and BL-8040-matching placebo is to be administered by slow SC injection of at least 2 minutes per syringe. If the total volume to be administered exceeds ~2 mL then dosing should be divided into two or more syringes to be administered. Each syringe, for the same treatment, should be administered to a different location within the same body area. At the PI's discretion, a different body area may be used for the same treatment, as needed. All subjects are to remain under surveillance for at least 2 hours after SC dosing.

To ensure blinding for the SC dosing, each subject will receive the same total injection volume in each SC dosing period. Subject' weight at check-in (Day -2 of Period 1) will be used to calculate the BL-8040 (and BL-8040-matching placebo) doses.

Prior to each SC injection, the site of injection will be examined.

Consistent use of the same body area of injection in all subjects for all SC dosing periods is preferred.

Moxifloxacin will be supplied as 400 mg moxifloxacin hydrochloride tablets. Moxifloxacin will be administered orally with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the tablet.

An unblinded pharmacist will be responsible for preparing BL-8040 or BL-8040-matching placebo and moxifloxacin tablets in individual unit dose containers for each subject and for each treatment to the blinded study personnel for administration as per the randomization scheme. Moxifloxacin dosing will be open-label.

Additional instructions for study drug preparation and administration will be provided in a separate pharmacy document.

Treatments are described as follows:

Treatment A: (Therapeutic)	1.25 mg/kg BL-8040 + BL-8040-matching placebo administered via SC injection
Treatment B: (Supratherapeutic)	2 mg/kg BL-8040 administered via SC injection
Treatment C: (Placebo Control)	BL-8040-matching placebo administered via SC injection
Treatment D: (Positive Control)	400 mg moxifloxacin (1 x 400 mg tablet) administered orally

For each subject, an appropriate volume of BL-8040-matching placebo will be used in Treatments A and C such that the total volume administered for each of Treatments A and C will be the same as the total volume injected in Treatment B.

All study drugs will be administered on Day 1 following an overnight fast. Hour 0 on Day 1 will be set as the start of dosing.

12.3 Dose Modification

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 11.3.

12.4 Treatment Compliance

Before and after the SC injection, the qualified designee will visually inspect the syringe to ensure that the subject has received the entire dose. In the case of an incomplete dosing in the opinion of the PI (or designee) and/or Sponsor, the subject may be withdrawn.

A qualified designee will be responsible for monitoring the administration of the timed oral (moxifloxacin) doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

12.5 Method of Treatment Assignment and Treatment Sequence

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding study drug, according to a randomization scheme.

Subjects will receive each of Treatments A, B, C, and D, in a pre-defined order according to the sequence scheme determined at randomization. The sequences to be used in the randomization are detailed in Table 4.

Early discontinued subjects will not be replaced.

Table 4: Design of Treatment Sequences

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A
5	B	C	A	D
6	C	D	B	A
7	A	B	D	C
8	D	A	C	B
9	C	A	B	D
10	A	D	C	B
11	B	C	D	A
12	D	B	A	C

Treatments A, B, C, and D are described in Section 12.2.

12.6 Blinding

This is a double-blind study in respect to BL-8040 and BL-8040-matching placebo dosing.

Moxifloxacin, the positive control, will be administered as open-label.

12.6.1 Maintenance of Randomization

A computerized randomization scheme will be created by a [redacted] statistician and it shall be considered blinded for BL-8040 dosing (as per the following).

The randomization is available only to the CRU pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug and to the Sponsor pharmacovigilance representative and other personnel that will be defined by the Sponsor. It will not be made available to other members of the Sponsor, [redacted] subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments.

12.6.2 Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the PI or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject or in the event of an interim analysis.

In the event of a medical emergency, it is requested that the PI or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the PI or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the PI or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained according to site procedures unless specified otherwise by the Sponsor.

12.6.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

12.7 Rescue Medication

In the event of an injection reaction, subjects may be treated with IV 100 mg hydrocortisone at the discretion of the PI.

Other steroids (oral, topical, and/or IV), anti-histamines, analgesics, or other medication (e.g., montelukast) according to the PI or designee judgment may also be administered to treat systemic reactions and injection site reactions. Negative chronotropic drugs, such as beta blockers, should be avoided as rescue medication.

A saline lock will be placed for at least approximately the first 2 hours following dosing to ensure rapid administration of rescue medication, if necessary.

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the cardiodynamic recording via ECG extractions from the Holter monitor and the PK blood samples are the critical parameters. Cardiodynamic recording via ECG extractions will be completed prior to the PK blood samples collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

When scheduled at the same time point, study procedures (excluding those at screening and check-in) will be performed in the following order (below) with regard to the prescribed time:

a. 12-lead safety ECGs
b. Cardiodynamic ECG recording extraction
c. Blood sample(s) collection (to be collected as close to the exact time point as possible)
d. Standardized meal or snack (meals and/or snacks must be completed at least 1 hour before any Holter recording extractions and/or safety ECG tracings)

Vital signs may be performed either before or after blood sample collection(s).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

13.1 Screening

Within 28 days prior to check-in, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be recorded. Each subject will have a 12-lead safety ECG, vital sign measurements (HR, blood pressure, temperature, and respiratory rate), clinical laboratory tests and additional tests as noted in Section 13.2.5, and physical examination.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination will be performed as outlined in the Study Events Flow Chart (Section 6). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and HR, will be measured as outlined in the Study Events Flow Chart (Section 6). Unscheduled vital signs may be taken at any other times, if deemed necessary.

Blood pressure and HR measurements will be performed with subjects in a supine position, except when they are seated or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

When scheduled postdose, vital signs will be performed within approximately 30 minutes of the scheduled time point.

13.2.3 ECG Monitoring

For study conduct, 12-lead ECGs will be classified as 12-lead safety ECGs or cardiodynamic ECGs and will be performed as outlined in the Study Events Flow Chart (Section 6).

ECG data will be will be obtained digitally using a Global Instrumentation (Manlius, New York, USA) M12R continuous 12-lead ECG digital recorder. The ECGs will either be collected via Bluetooth and available for real time safety review or will be stored as a continuous 12-lead ECG recording on a flash card (Holter recording for cardiodynamic ECG extraction) and are not available for review until the data is downloaded after the 24-hour recording has ended.

A subject will be withdrawn from the study by the PI or designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest. In this case, if deemed clinically significant per PI, this should be reported within the CRF as an AE and the reason for discontinuation should be due to AE.

13.2.3.1 12-Lead Safety ECGs

Single 12-lead safety ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

12-lead safety ECGs will be collected with subjects in a supine position in a quiet environment. All ECG tracings will be reviewed by the PI or designee. Intervals for 12-lead safety ECGs will be classified as normal, not clinically significant, or clinically significant. The 12-lead safety ECG data, including all time points, will be recorded in the CRF and be used to determine subject eligibility, evaluate general cardiac safety parameters for subjects during the study and to evaluate cardiac related AEs.

When scheduled postdose, ECGs will be performed within approximately 30 minutes of the scheduled time point.

13.2.3.2 Cardiodynamic ECGs

Holter monitors will be used to collect continuous 12-lead ECG data for the purpose of collecting cardiodynamic ECGs. Recording will be started and stopped at logistically optimal times to ensure that all scheduled time points are collected.

ECGs will be obtained as replicate (up to 10) 12-lead ECGs within each extraction window at each time point and will be downloaded from the M12R flash card on Day 1 of each treatment period. Replicate 12-lead ECGs will be extracted within a 5-minute time window around the scheduled time points as outlined in the Study Events Flow Chart (Section 6) but prior to the PK blood sample collection.

Timing and recording technique for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other participants, etc.) for at least 10 minutes prior to each ECG extraction and throughout the duration of the extraction to allow for quality ECG extraction. All ECG extractions should occur in a 5-minute time window prior to the PK blood samples which should be collected as close to the exact scheduled/nominal time point as possible. If extracted ECGs from targeted time points are artefactual or of poor quality, analyzable 14-second ECGs will be extracted as close as possible to the targeted time points.

Nominal time of the ECG recording will be used for the cardiodynamic analysis.

The 12-lead Holter and ECG equipment will be supplied and supported by [redacted] The continuous 12-lead digital ECG data will be stored onto Secure Digital™ memory cards. ECGs to be used in the analyses will be selected by pre-determined time points as outlined in the Study Events Flow Chart (Section 6), and will be read centrally by the Core ECG Laboratory.

The principles to be followed at the Core ECG Laboratory and a brief description of ECG analysis methods utilized by [redacted] core laboratory are described as follows:

- ECG analysts are blinded to the subject, visit, and treatment randomization.
- Baseline and on-treatment ECGs for individual subjects will be analyzed for 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 for analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by the [redacted] core laboratory.

13.2.3.2.1 TQT Plus ECG Extraction Technique

The core laboratory will use TQT Plus, an advanced computer-assisted and statistical process utilized to extract ECGs from continuous 24-hour recordings collected in TQT studies. During protocol-specified ECG extraction windows, 10-second digital 12-lead ECG tracings will be extracted from continuous recordings. The TQT Plus method enables the extraction of

a high-quality data set by identifying periods of recordings with the lowest available HR variability and noise.

The ECGs will be extracted according to the following principles:

- The actual times of dosing, extraction windows, and PK sampling will be communicated to the central ECG laboratory by the CRU personnel.
- The TQT Plus process will identify periods of stable HR on the continuous 12-lead ECG tracing within the 5-minute extraction window. Stability will be defined as variation in the HR and other ECG parameters from beat-to-beat lower than a predefined threshold. If the TQT Plus method results in a low number of consecutive, readable cardiac cycles in the 5-minute time point, the time point will be fully reviewed manually.
- Replicate, non-overlapping 10-second ECGs will be extracted in close succession within each extraction window.

13.2.3.2.2 Expert-Precision QT Analysis

At each nominal time point specified in the protocol, up to 10 ECG replicates will be extracted with TQT Plus methods. All readable cardiac cycles from these ECG replicates will be assessed for multiple quality metrics, including beat stability, HR changes, noise, and other parameters, and will be categorized into high and low confidence rank. All low confidence beats will be fully reviewed and adjudicated manually by ECG technicians using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis.

The primary analysis lead will be Lead II. If Lead II is not analyzable, then the primary lead of analysis will be changed to Lead V2 for the subject's entire data set. If Lead V2 is not analyzable, then Lead V5 will be used for the subject's entire data set. If both alternate leads cannot be used, the data may be deemed non-analyzable or the [redacted] cardiologist may decide the most appropriate lead to use for the subject's entire data set. The lead used for analysis will be listed in the data listings transferred from [redacted]

ECG morphology analysis and measurement of PR and QRS intervals will be fully performed manually in 3 of the 10 ECG replicates at each time point. Final quality control and diagnostic interpretations will be performed by the cardiologist. When the results for each time point are compiled in the final data set, the comparison will be made between ECG parameters from the 3 manually reviewed ECGs versus the 10 ECG replicates for quality control purposes. If significant differences are found, the entire time point will be reviewed manually.

13.2.3.2.3 Cardiodynamic ECG Assessment

A continuous 12-lead ECG and Holter data acquisition will be in place as outlined in the Study Events Flow Chart (Section 6). The continuous recording from Day -1 of Period 1 will be used for the Optimized QTcI Calculation, but not for standard ECG extractions.

The following ECG parameters will be measured and calculated: HR, RR, PR, QT, QTcF, QTcI, and QRS. Changes in ECG morphology will also be assessed.

The primary analysis will be based on concentration-QTc modeling of the relationship between BL-8040 and ΔQTcI with the intent to exclude an effect >10 msec at clinically relevant plasma concentrations of BL-8040. The relationship between BL-8040 plasma concentration and ΔQTcF will also be explored.

In addition, the effect of BL-8040 on ΔΔQTcI, ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS will be evaluated at each postdose time point ('by time point' analysis). An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTc (QTcI and QTcF), as well as an analysis of new ECG morphology changes.

Assay sensitivity will be evaluated by concentration-QTc analysis of the effect on ΔQTcI of moxifloxacin using a similar model as for the primary analysis, as will be detailed in the SAP.

13.2.4 Height, Body Weight, and BMI

Height and body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 6).

The Screening height measurement will be used for BMI calculations throughout the study.

13.2.5 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation
- Prothrombin time/international normalized ratio and activated partial thromboplastin time

Urinalysis
- pH
- Specific gravity
- Protein ***
- Glucose
- Ketones
- Bilirubin
- Blood ***
- Nitrite***
- Urobilinogen
- Leukocyte esterase ***

Serum Chemistry *
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Magnesium
- Chloride
- Glucose (fasting)
- Creatinine **

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates §
  - Opioids
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of early discontinuation or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.

** At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, WBCs, bacteria, casts, and epithelial cells) will be performed.

13.2.6 Adverse Events

13.2.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

13.2.6.2 Monitoring

Subjects will be monitored from the time of signing the ICF for adverse reactions to the study formulations and/or procedures. Prior to release, subjects will be asked how they are feeling. At each subsequent visit and at the beginning of subsequent periods, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a licensed health care professional, either at [redacted] or at a nearby hospital emergency room where appropriate medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown (lost to follow-up).

13.2.6.3 Reporting

All AEs that occurred during this clinical study will be recorded. The PI or designee will review each event and assess its relationship to drug treatment (related or not related). Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

Mild	The AE is easily tolerated and does not interfere with daily activity.
Moderate	The AE interferes with daily activity, but the subject is still able to function. Medical intervention may be considered.
Severe	The AE is incapacitating and requires medical intervention.

13.2.6.4 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail ([redacted]) within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

13.3.1.1 BL-8040 (Motixafortide)

For all subjects, blood samples for the determination of BL-8040 will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

The analytical laboratory measuring plasma concentrations of BL-8040 will be unblinded to the samples as their analyses will be related to treatments.

13.3.1.2 Moxifloxacin

For all subjects, blood samples for the determination of moxifloxacin will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

The analytical laboratory measuring plasma concentrations of moxifloxacin will be unblinded to the samples as their analyses will be related to treatments. Only samples from the period where subjects received moxifloxacin are planned to be analyzed.

13.3.2 Pharmacokinetic Parameters

The following PK parameters for plasma BL-8040 and moxifloxacin will be calculated, as appropriate:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
CL/F:	Apparent total plasma clearance after extravascular administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after extravascular administration, calculated as Dose/(AUC0-inf x Kel).

No value for Kel, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

13.3.3 Analytical Method

Samples from all subjects receiving active study drug(s) will be assayed even if the subjects do not complete the study. Samples collected for potential analysis will be assayed only if deemed necessary.

Samples will be analyzed for plasma BL-8040 and moxifloxacin using validated bioanalytical methods.

13.4 Pharmacodynamic Assessments

Blood samples for PD analysis (e.g., CD34+ enumeration, RO) will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

13.5 Future Research

Any residual plasma from the PK and/or PD samples will be stored by the Sponsor or bioanalytical facility for 5 years after the last dosing and may be used for future analyses (e.g., PK, PD). Tubes will be identified with a barcode using an appropriate label. No diseases/conditions, deoxyribonucleic acid (DNA), or ribonucleic acid (RNA) will be the focus of these analyses. The analyses will only focus on PK, PD, metabolites, and/or biomarkers. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and PK and statistical analyses of the data will have access to the samples and/or the data that resulted from the analysis, if performed. By signing the ICF, subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the CRU staff to requested destruction of the residual samples after the PK assessments required to meet the objective of the study are completed. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

13.6 Blood Volume Drawn for Study Assessments

Table 5: Blood Volume During the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, and serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	16	16
On-study hematology, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time), and coagulation	9	16	144
Additional on-study CBC samples	21	4	84
Blood for BL-8040 PK (including samples for potential analysis)	44	2	88
Blood for moxifloxacin PK (including samples for potential analysis)	18	3	54
Blood for PD analysis (CD34+)	24	5	120
Blood for PD analysis (RO)	18	4	72
Total Blood Volume (mL)→			578 **

* Represents the largest collection tube that is expected to be used for this sample (a smaller tube may be used).

** If additional safety, PK, and/or PD analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to [redacted] SOPs, which are written based on the principles of GCP.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by [redacted] and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate. A separate Clinical Statistical Analysis Plan, describing the details of the statistical analysis, will be prepared by [redacted]

14.1 Sample Size Determination

With approximately 40 randomized subjects, it is estimated that at least 26 evaluable subjects will have data from all treatment periods. A sample size of 26 evaluable subjects will provide more than 90% power to exclude that BL-8040 causes more than a 10 msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% CI of the model predicted QTc effect (ΔΔQTcI) at the observed geometric mean Cmax of BL-8040 in the study. This power is estimated approximately using a simple paired t-test. The calculation assumes a one-sided 5% significance level, a small underlying effect of 3 msec for BL-8040 and 0 msec for placebo, and a standard deviation (SD) of ΔQTcI of 8 msec for each treatment. 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 and Ferber et al, 2015, and consistent with the experiences from 25 recent TQT studies.

14.1.1 Sample Size Determination for Assay Sensitivity

Demonstration of assay sensitivity with concentration-QTc will be confirmed by demonstrating that the predicted QTc effect (ΔΔQTcI) of a single dose of 400 mg moxifloxacin exceeds 5 msec, i.e., the lower bound of the 2-sided 90% CI of the predicted QTc effect should exceed 5 msec. In a similarly designed, recent crossover study with 24 healthy subjects (on-file data, [redacted] the standard error (SE) for the prediction of the QTc effect (ΔΔQTcF) of moxifloxacin based on the concentration-QTc analysis was 1.24 msec. The SD of ΔQTcF in the referred study was 5.4 msec based on the by-time point 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 x 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 0.59 required to guarantee a power of at least 90% in a paired t-test situation with a sample size of 26 evaluable subjects. In other words, based on this calculation, a power of at least 90% for 26 evaluable subjects will be obtained as long as the variability of ΔQTcI, as measured by its within-subject SD, does not exceed the 7.5 msec observed in the referred study (i.e., 139% 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 (Huang et al, 2019).

14.2 Population for Analyses

Safety Population: All subjects who received at least one dose of any of the study drugs (BL-8040, placebo, or moxifloxacin) will be included in the safety analysis.

PK Population: All randomized subjects who receive a dose of BL-8040 or moxifloxacin and provide at least 1 evaluable PK concentration for BL-8040 or moxifloxacin.

QT/QTc Population: All subjects in the Safety Population with measurements at Baseline as well as on-treatment with at least 1 postdose time point with a valid ΔQTcI value. The QT/QTc population will be used for the by-time point and categorical analyses of cardiodynamic ECG parameters.

PK/QTc Population: All subjects who are in both the PK and QT/QTc Populations with at least 1 pair of postdose PK and ΔQTcI data from the same time point, as well as subjects in the QT/QTc Population who received placebo. The PK/QTc Population will be used for the concentration-QTc analysis. PK/QTc population will be defined for BL-8040 and for moxifloxacin.

14.3 Cardiodynamic Analyses

Details of the cardiodynamic analysis will be provided separately in a SAP.

14.4 Pharmacokinetic Analyses

14.4.1 Descriptive Statistics

The plasma BL-8040 and moxifloxacin concentrations and the PK parameters listed in Section 13.3.2 will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

14.5 Pharmacodynamic Analysis

Details of the PD analysis (e.g., CD34+, RO) will be provided separately and may be reported in a separate document outside of the clinical study report (CSR).

14.6 Safety Analyses

All safety data will be populated in the individual CRFs. All CRF data will be listed by subject in the final report.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at [redacted] and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data

listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including safety ECGs, vital signs assessments, and clinical laboratory results (including CBC) will be summarized by treatment and time point of collection.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results.

Concomitant medications will be listed by subject and coded using the most current version of WHO drug dictionary available at [redacted] Medical history will be listed by subject.

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

This protocol will be reviewed by [redacted] IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines, and may be reached at:

[redacted]

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], November 2016).

15.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

15.1.4 Confidentiality

All members of the PI's staff have signed confidentiality agreements with [redacted]. By signing this protocol, the PI and [redacted] staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The PI must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the PI who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the

responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

15.2 Termination of the Study

[redacted] reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

15.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at [redacted] relevant to the quality of this study. Designated personnel of [redacted] will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, and GCP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The CSR will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

[redacted] will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of BL-8040 and BL-8040-matching placebo to allow completion of this study. [redacted] will provide sufficient quantities of sterile 0.45% saline (half saline) for injection (use for the reconstitution of BL-8040 and BL-8040-matching placebo) and moxifloxacin hydrochloride tablets to allow completion of the study. [redacted] will also provide nizatidine oral solution, cetirizine hydrochloride tablets, acetaminophen tablets, and montelukast sodium tablets. Rescue medication will also be provided by [redacted] The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by [redacted] returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased by [redacted] will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

15.6 Data Handling and Record Keeping

[redacted] standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor in the format as decided between [redacted] and the Sponsor (e.g., compact disc, flashdrive, secure file transfer protocol). This will be documented in the data management plan (if applicable).

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by [redacted] until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

All unpublished information given to [redacted] by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

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