STATISTICAL ANALYSIS PLAN

AUTHOR(S):	[redacted]
PROJECT MANAGER:	[redacted]
SAP VERSION:	Final 1.1
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SPONSOR:	Lumosa Therapeutics Co., Ltd. 4F, No 3-2, Park Street, Nangang Dist., Taipei 11503 Taiwan, Republic of China
STUDY TITLE:	A Double-Blind, Randomized, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of LT3001 Drug Product and Drug-Drug Interaction in Healthy Adult Subjects
PHASE OF STUDY:	Phase 1
PROTOCOL NUMBER:	LT3001-105
PROTOCOL VERSION/DATE:	V1.4/11Mar2021

APPROVALS

Revision History

Version	Changes
1.0	Original document
1.1	Updated to reflect protocol V1.4 – Correct SoA and paragraph about platelet function added

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1. ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	Adverse event
Ae_{x-y}	Amount of drug excreted in urine within a collection interval (x to y hours)
Ae_{0-24}	Total amount of drug excreted in urine over the entire collection period (0 to 24 hours)
aPTT	Activated partial thromboplastin time
ATC	Anatomical/Therapeutic/Chemical
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from zero to infinity
AUC_{0-t}	Area under the concentration-time curve from zero up to the last timepoint with a measurable concentration
$AUC_{0-\tau}$	Area under the concentration-time curve over the dosing interval τ at steady-state
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood Pressure
Cav	Mean steady-state drug concentration
CL	Total body clearance of the drug from plasma
CL_R	Renal clearance
C_{max}	Maximum observed plasma drug concentration
C_{min}	Trough plasma concentration
CRA	Clinical research associate
CS	Clinically significant
CSR	Clinical synopsis report
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
GM	Geometric mean
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IV	Intravenous
λz	Apparent first-order terminal elimination rate constant
LLQ	Lower limit of quantification

Abbreviation or Special Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
n	Number of observations
PD	Protocol deviation
PK	Pharmacokinetic
PT	Prothrombin time OR Preferred term
R_{acc}	Accumulation ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SoA	Schedule of activities
SOC	System organ class
$t_{1/2}$	Elimination half life
TEAE	Treatment-emergent adverse event
TID	Three times a day
t_{max}	Time to maximum observed drug concentration
tt	Thrombin time
V_{ss}	Apparent volume of distribution during the steady state
Vz	Apparent volume of distribution during the terminal phase
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to prospectively outline in detail the data derivations, statistical methods, and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the protocol LT3001-105, dated 17 November 2020.

This SAP is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. The statistical analysis methods presented in this document will amend and/or supersede the statistical analysis methods described in the protocol. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the CSR.

2.1. Responsibilities

Inference, Inc will perform the statistical analyses for all clinical data collected. Inference, Inc is responsible for production and quality control of all datasets, tables, figures, and listings.

2.2. Timing of Analyses

Only one final analysis after all subjects complete the study and subsequent database lock will be performed.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

- Part A: To determine the safety, tolerability, and PK of a 3-day TID use of LT3001 drug product, when administered as an IV infusion q3h between each dose within one day in healthy subjects (with 50% Chinese subjects)
- Part B: To determine the safety and PK of LT3001 when coadministered with aspirin, clopidogrel, apixaban, or dabigatran.

3.2. Endpoints

Part A Endpoints:

- Nature and severity of adverse events (AEs) and number of subjects with AEs
- Changes from baseline in physical examination, vital signs, electrocardiogram (ECG) assessment, oximetry, coagulation, and clinical laboratory tests
- Plasma PK parameters of LT3001
- Urine PK parameters of LT3001
- Effects of LT3001 drug product on systolic and diastolic blood pressure (SBP/DBP), prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT)

Part B Endpoints:

- Nature and severity of AEs and number of subjects with AEs
- Changes from baseline in physical examination, vital signs, ECG assessment, bleeding time, coagulation, and clinical laboratory tests
- Plasma PK parameters of LT3001
- Plasma PK parameters of aspirin, clopidogrel, apixaban and dabigatran

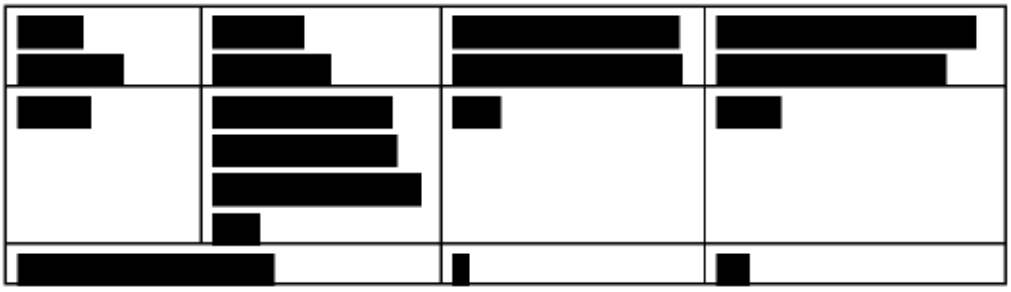
4. STUDY DESIGN

This study is a two-part study. Part A is double-blind, placebo-controlled, and will examine the safety and PK profiles of multiple doses of LT3001 drug product in healthy subjects. Part B is open-label and will assess the safety and PK of LT3001 when coadministered with aspirin, clopidogrel, apixaban or dabigatran.

The statistical analyses for each of the two parts will be done separately.

Part A

Approximately 16) healthy subjects will be randomized in a 3:1 ratio to receive either LT3001 drug product or placebo administered as a 15-minute intravenous (IV) infusion. Each subject will receive three doses, administered 3 hours apart, on Days 1, 2, and 3. The first 4 subjects will be "sentinel subjects," with 2 subjects assigned to receive LT3001 drug product and the other 2 subjects assigned to receive placebo. The Investigator will review all available safety data from the sentinel subjects. If considered safe to do so, the remaining subjects will be dosed.



After all healthy subjects complete study procedures of Part A, the safety review meeting will be held by the Investigator and the sponsor medical monitor (or designee) to review all available safety and blood PK data of all subjects and determine whether one or more of the following should occur:

- Enrollment of subjects of Part B will proceed
- More subjects should be enrolled, up to a maximum of 16 subjects in LT3001 drug product group, based on safety and blood PK data

- Refinement of PK sampling times is recommended
- A protocol amendment is recommended.

Part B

Part B is open-label without placebo control. Approximately 48 subjects will be sequentially enrolled into four cohorts with 12 subjects in each cohort. The first 3 subjects of each cohort will be "sentinel subjects." After each sentinel subject completes the first day of combination treatments, the Investigator will review all available safety data from the sentinel subjects. If considered safe to do so, each sentinel subject will receive the remaining combination treatments.

Each Cohort of Part B	Sentinel Subjects	Remaining Subjects
Number of Subjects	3	9

In Cohort 1, each subject will receive a single 15-minute infusion of LT3001 [redacted] on Day 1. Each subject will also receive multiple-dose aspirin as follows: a loading dose of 325 mg aspirin on the morning of Day 2 followed by a daily maintenance dose of 81 mg aspirin on Days 3 through 8. On the morning of Day 6, the dose of aspirin will be followed by the first dose of the multiple doses of LT3001 ([redacted]). Subjects will receive 9 doses of LT3001 on Days 6 through 8 (TID q3h). The dosing schema for Cohort 1 is as follows:

In Cohort 2, each subject will receive a single 15-minute infusion of LT3001 [redacted] on Day 1. Each subject will receive multiple-dose clopidogrel as follows: a loading dose of 300 mg clopidogrel on Day 2 followed by a daily maintenance dose of 75 mg clopidogrel on Days 3 through 9. On Day 7, the dose of clopidogrel will be followed by the first dose of the multiple doses of LT3001 ([redacted]). Subjects will receive 9 doses of LT3001 on Days 7 through 9 (TID q3h). The dosing schema for Cohort 2 is as follows:

In Cohort 3, each subject will receive a single 15-minute infusion of LT3001 [redacted] on Day 1. Each subject will receive multiple-dose apixaban as follows: 5 mg apixaban twice daily (BID) every 12 hours (q12h) on Days 2 through 7. Given that the half-life of apixaban is 9 to 14 hours, the 3-day apixaban BID treatment allows for reaching over 5 half-lives and 97% steady state of apixaban before the coadministration of apixaban and LT3001. On Day 5, the first dose of apixaban will be followed by the first dose of the multiple doses of LT3001 [redacted]). Subjects will receive 9 doses of LT3001 on Days 5 to 7 (TID q3h). The dosing schema for Cohort 3 is as follows:

[redacted]

In Cohort 4, each subject will receive a single 15-minute infusion of LT3001 [redacted] on Day 1. Each subject will receive multiple-dose dabigatran as follows: 110 mg dabigatran BID (q12h) on Days 2 through 7. Given that the half-life of dabigatran is 12 to 17 hours, the 3-day dabigatran BID treatment allows for reaching over 4 half-lives and 94% steady state of dabigatran before the coadministration of apixaban and LT3001. On Day 5, the first dose of dabigatran will be followed by the first dose of the multiple doses of LT3001 ([redacted] infusion). Subjects will receive 9 doses of LT3001 on Days 5 to 7 (TID q3h).

[redacted]

4.1. Sample Size Justification

Sample sizes were not based on statistical considerations. Sixteen subjects in Part A, and 12 subjects per cohort in Part B are deemed sufficient to achieve the study objectives.

4.2. Schedule of Assessments (SoA)

The following assessments will be performed in this study:

Schedule of Activities for Part A

Procedures	Day -30 to Day -2	Day -1	Day 1				Day 2				Day 3				Day 4
		Hour[p]	1	4	7	13	25	28	31	37	49	52	55	61	73
	Screening Period		Dose 1	Dose 2	Dose 3		Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9		EOS[o]
Informed consent	X														
Demographics	X														
Body Weight	X	X													
Medical history	X														
Physical examination	X		X				X				X				X
Vital sign[a]	X[a]	X[a]	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]		X[a]	X[a]	X[a]		X[a]
Coagulation parameters[b]	X[c]	X[c]	X[b]				X[b]						X[b]		X[b]
Platelet function test		X[r]	X[s]										X[t]		X
Hematology test[d]	X[c]	X[c]					X								X
Clinical chemistry test[e]	X[c]	X[c]					X								X
Urinalysis[f]	X[c]	X[c]					X								X
Urine drug/cotinine/alcohol test	X[c]	X[c]													
Virology test[g]	X														
Serum pregnancy test[h]		X[h]													
12-lead ECG assessment[i]	X		X[i]				X[i]				X[i]				
Pulse oximetry		X	X[j]	X[j]	X[j]		X[j]	X[j]	X[j]		X[j]	X[j]	X[j]		
Eligibility assessment	X	X													
Randomization			X												
LT3001 drug product/ placebo[k]			[redacted]												
PK blood sample															

Procedures	Day -30 to Day -2	Day -1	Day 1				Day 2				Day 3				Day 4
		Hour[p]	1	4	7	13	25	28	31	37	49	52	55	61	73
	Screening Period		Dose 1	Dose 2	Dose 3		Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9		EOS[o]
PK urine sample			X[u]			X[u]	X[u]			X[u]	X[u]			X[u]	X[u]
Discharge															X
Prior and concomitant medication	X	X	X												
Adverse event			X												

ECG = electrocardiogram; EOS = end-of-study; PK = pharmacokinetic

a. Vital signs will include body temperature, blood pressure, respiratory rate, and heart rate. Measurements will be made after the subject has rested in a supine position for at least 3 minutes. Blood pressure will be assessed in seated and supine position at predose and 60 minutes after dosing/infusion, only supine position at 20 minutes after dosing/infusion. Vital signs will be assessed at screening visit, Day 1 to Day 3 (each dosing period at pre-dose, 20 minutes and 1 hour after infusion is initiated), and Day 4.

b. Coagulation parameters that include PT/INR, aPTT, and TT will be assessed at screening visit, Day -1, at 15 minutes after initiation of the infusion of Dose 1 on Day 1, Dose 4 on Day 2, Dose 9 on Day 3, and Day 4.

c. If these are performed on Day -4 to Day -2, need not to be reassessed on Day -1.

d. Hematology tests will include hemoglobin (Hg), red blood cell count (RBC), mean corpuscular volume (MCV), hematocrit (Hct), mean corpuscular hemoglobin (MCH), white blood cell count (WBC), differential (WBC-DC), and platelets.

e. Clinical chemistry tests will include blood urea nitrogen (BUN), creatinine, fasting blood glucose, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin, total proteins, albumin/globulin ratio, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), bicarbonate, uric acid, creatine kinase (CK), cholesterol, triglycerides, free iron, and ferritin.

f. Urinalysis will include dipstick urinalysis and microscopic examination.

g. Virology tests will include human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody and COVID-19 antibody.

h. Serum pregnancy test will be performed in female subjects of childbearing potential within 24 hours prior to the 1st study drug administration.

i. A 12-lead ECG assessment will be obtained at screening visit and at pre-dose and 1 hour after infusion is initiated of the 1st dose of Day 1, Day 2, and Day 3 (Dose 1, Dose 4, and Dose 7)

j. Pulse oximetry continuous monitoring will be performed from predose up to 1 hour after each infusion is initiated. Oximetry will be recorded at pre-dose and 20 minutes after infusion is initiated (end of infusion).

k. Subjects will receive LT3001 drug product/ placebo treatment as continuous 15-minute IV infusions 3 times each day on Day 1 to Day 3 with 3 hours between doses.

l. PK blood samples will be collected f[redacted] 40±1 minutes after infusion is initiat

m. PK blood samples will be collected f[redacted] (Dose 7) at pre-dose and 15±1 min a

n. PK urine samples will be collected on Day 1 at predose, and on Day 1, Day 2, and Day 3, over the intervals 0 to ≤12 hours and 12 to ≤ 24 hours after the infusion is initiated.

o. All subjects who receive at least one dose will complete the end-of-study (EOS) visit (within 3 to 72 hours after the last study drug administration).

p. A 30-minute window is allowed for non-PK procedures

q. Physical examination will be performed at screening visit, predose on Day 1, Day 2 and Day 3 and Day 4.

r. Platelet function test will be measured at pre-dose on Day -1.

s. Platelet function test will be measured on the first dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 1.

t. Platelet function test will be measured on the last dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 3.

Schedule of Activities for Part B, Cohort 1

Procedures	Screening Period		Treatment Period														Follow-up	ET [s]
	Day -30 to -2	Day -1 Hour [n]	Day 1 1	Day 2 25	Day 3 49	Day 4 73	Day 5 97	Day 6 121	Day 6 124	Day 6 127	Day 7 145	Day 7 148	Day 7 151	Day 8 169	Day 8 172	Day 8 175	Day 15 +/- 1	
Informed consent	X																	
Urine drug/cotinine/alcohol test	X	X [t]																
Virology test [a]	X																	
Demographics [b]	X	X																
Medical and surgical history	X																	
Check In		X																
Serum pregnancy test [c]		X																
Aspirin [d]				X	X	X	X	X			X			X				
LT3001 drug product			X [t]					X	X	X	X	X	X	X	X	X		
Physical examination [e]	X		X				X									X	X	X
Vital sign [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG assessment [g]	X	X	X	X	X	X	X	X			X			X			X	X
PK blood sample of LT3001			[redacted]															
PK blood sample of Aspirin [j]																		
Platelet function test		X [k]					X [k]	X [l]								X [m]	X	X
Coagulation [n]	X	X [t]					X [k]	X [l]								X [m]	X	X
Hematology test [o]	X	X [t]					X									X	X	X
Clinical chemistry test [p]	X	X [t]					X									X	X	X
Urinalysis [q]	X	X [t]					X									X	X	X
Discharge															X			
Prior and concomitant medication	X	X	X															
Adverse event			X															

ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic

a. Virology tests will include HIV antibody, HBsAg, hepatitis C virus antibody, and COVID-19 antibody.

b. Demographics will include age, gender, height, body weight, body mass index (BMI) and race. On Day -1, only body weight will be measured.

c. Serum pregnancy test will be performed in female subjects of childbearing potential within 24 hours prior to the first drug treatment on Day 1.

d. Subjects will receive aspirin after breakfast. The dose of aspirin on Day 6, Day 7 and Day 8 will be followed immediately by 0.025 mg/kg LT3001 administered as a 15-minute IV infusion.

e. Physical examination will be performed at screening visit, predose on Day 1, the end of aspirin single treatment on Day 5, the end of combination treatment on Day 8 and follow-up visit on Day 15

f. Vital signs will include body temperature, blood pressure, respirtory rate, and heart rate. Measurements will be made after the subject has rested in a supine position for at least 3 minutes. Blood pressure will be assessed in seated and supine position at predose and 60 minutes after dosing/infusion, only supine position at 20 minutes after dosing/infusion. Vital signs will be assessed at screening visit, Day 1 to 5 (pre-dose), Day 6 to Day 8 (each LT3001 dosing period at pre-dose, 20 minutes and 60 minutes after infusion is initiated), and follow-up visit on Day 15.

g. A 12-lead ECG assessment will be performed at screening visit and at pre-dose and 1 hour after taking aspirin on Day 2 to Day 5, one hour after the infusion is initiated of the first dose of LT3001 on Day 6 to Day 8 and follow-up visit on Day 15.

h. PK blood samples of LT3001 will be [redacted] 30±1, 45±1, and 60±5 minutes after

i. PK blood samples of LT3001 will be [redacted] infusion is initiated (end of infusion)

j. PK blood samples of aspirin will be [redacted] postdose.

k. Platelet function test and coagulation test will be measured at pre-dose on Day -1 and at 15 min and 6 hour15 min after the last dose of aspirin single treatment on Day 5.

l. Platelet function test and coagulation test will be measured on the first dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 6.

m. Platelet function test and coagulation test will be measured on the last dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 8.

n. Coagulation parameters will include PT, INR, aPTT, and TT.

o. Hematology tests will include Hb, RBC, MCV, Hct, MCH, WBC, WBC-DC, and platelets.

p. Clinical chemistry tests will include BUN, creatinine, fasting blood glucose, ALP, ALT, AST, GGT, total bilirubin, total proteins, albumin/globulin ratio, Na, K, Cl, Ca, bicarbonate, uric acid, CK, cholesterol, triglycerides, free iron, and ferritin.

q. Urinalysis will include dipstick urinalysis and microscopic examination.

r. When the urine drug/cotinine/alcohol tests and/or clinical laboratory tests including coagulation, hematology and clinical chemistry are performed on Day -4 to Day -2, these tests need not be repeated on Day -1.

s. In the event of early termination (ET), a randomized subject will complete the ET procedures. Based on the Investigator's discretion, the collection of PK blood samples of LT3001 and/or aspirin can be exempted if the subject did not receive the indicated study drug.

t. A single dose of LT3001 drug product will be given on Day 1

u. A 30-minute window is allowed for non-PK procedures

Schedule of Activities for Part B, Cohort 2

Procedures	Screening Period	Treatment Period																Follow-up	ET [r]
	Day -30 to -2	Day -1 Hour[a]	Day 1 1	Day 2 25	Day 3 49	Day 4 73	Day 5 97	Day 6 121	Day 7 145	Day 7 148	Day 7 151	Day 8 169	Day 8 172	Day 8 175	Day 9 193	Day 9 196	Day 9 199	Day 10 217	Day 16 +/- 1	
Informed consent	X																			
Urine drug/cotinine/alcohol test	X	X [r]																		
Virology test [a]	X																			
Demographics [b]	X	X																		
Medical and surgical history	X																			
Check In		X																		
Serum pregnancy test [c]		X																		
CYP2C19 genotyping	X																			
Clopidogrel [d]				X	X	X	X	X	X			X			X					
LT3001 drug product			X[o]						X	X	X	X	X	X	X	X	X			
Physical examination [e]	X		X					X									X		X	X
Vital sign [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG assessment [g]	X	X	X	X	X	X	X	X	X			X			X				X	X
PK blood sample of LT3001			[redacted]																	
PK blood sample of clopidogrel [i]																				
Platelet function test		X [k]						X [k]	X [l]								X [m]		X	X
Coagulation [n]	X	X [r]						X [k]	X [l]								X [m]		X	X
Hematology test [o]	X	X [r]						X									X		X	X
Clinical chemistry test [p]	X	X [r]						X									X		X	X
Urinalysis [q]	X	X [r]						X									X		X	X
Discharge																		X		
Prior and concomitant medication	X										X									
Adverse event											X									

ECG = electrocardiogram, ET = early termination, PK = pharmacokinetic

a. Virology tests will include HIV antibody, HBsAg, hepatitis C virus antibody, and COVID-19 antibody.

b. Demographics will include age, gender, height, body weight, BMI and race. On Day -1, only body weight will be measured.

c. Serum pregnancy test will be performed in female subjects of childbearing potential within 24 hours prior to the first drug treatment on Day 1.

d. The dose of clopidogrel on Day 7, Day 8 and Day 9 will be followed immediately by 0.025 mg/kg LT3001 administered as a 15-minute IV infusion.

e. Physical examination will be performed at screening visit, pre-dose on Day 1, the end of clopidogrel single treatment on Day 6, the end of combination treatment on Day 9 and follow-up visit on Day 16.

f. Vital signs will include body temperature, blood pressure, respiratory rate, and heart rate. Measurements will be made after the subject has rested in a supine position for at least 3 minutes. Blood pressure will be assessed in seated and supine position at predose and 60 minutes after dosing/infusion, only supine position at 20 minutes after dosing/infusion. Vital signs will be assessed at screening visit, Day 1 to 6 (pre-dose), Day 7 to Day 9 (each LT3001 dosing period at pre-dose, 20 minutes and 60 minutes after infusion is initiated) and follow-up visit on Day 16.

g. A 12-lead ECG assessment will be performed at screening visit and at pre-dose and 1 hour after taking clopidogrel on Day 2 to Day 6, and after 1 hour after the infusion is initiated of the first dose of LT3001 on Day 7 to Day 9 and follow-up visit on Day 16.

h. PK blood samples of LT3001 will be collected on Day 1, on the first dose of LT3001 on Day 7 and the 3rd dose of Day 9 at pre-dose, 5±1, 10±1, 15±1, 20±1, 25±1, 30±1, 45±1, and 60±5 minutes after infusion is initiated.

i. PK blood samples of LT3001 will be [redacted] infusion is initiated (end of infusion)

j. PK blood samples of clopidogrel will [redacted] Day 6 and Day 9 will be collected on [redacted] dosing on Day 7) A 5-minute window

k. Platelet function test and coagulation test will be measured at pre-dose on Day -1 and at 15 min and 6 hour15 min after the last dose of clopidogrel single treatment on Day 6

l. Platelet function test and coagulation test will be measured on the first dose of LT3001 on Day 7 at 15 min after infusion is initiated (end of infusion)

m. Platelet function test and coagulation test will be measured on the last dose of LT3001 on Day 9 at 15 min after infusion is initiated (end of infusion)

n. Coagulation parameters will include PT, INR, aPTT and TT.

o. Hematology tests will include Hb, RBC, MCV, Hct, MCH, WBC, WBC-DC, and platelets.

p. Clinical chemistry tests will include BUN, creatinine, fasting blood glucose, ALP, ALT, AST, GGT, total bilirubin, total proteins, albumin/globulin ratio, Na, K, Cl, Ca, bicarbonate, uric acid, CK, cholesterol, triglycerides, free iron, and ferritin.

q. Urinalysis will include dipstick urinalysis and microscopic examination.

r. When the urine drug/cotinine/alcohol tests and/or clinical laboratory tests including coagulation, hematology and clinical chemistry are performed on Day -4 to Day -2, these tests need not be repeated on Day -1.

s. In the event of early termination (ET), a randomized subject will complete the ET procedures. The collection of PK blood samples of LT3001 and/or clopidogrel can be exempted based on the Investigator's discretion if the subject did not receive the indicated study drug.

t. A single dose of LT3001 drug product will be given on Day 1.

u. A 30-minute window is allowed for non-PK procedures.

Schedule of Activities for Part B, Cohort 3

Procedures	Screening Period		Treatment Period																		Follow-up	
	Day -30 to -2	Day -1	Day 1	Day 2	Day 3		Day 4		Day 5			Day 6				Day 7			Day 8	Day 14	ET[s]
		Hour[m]	1	25	37	49	61	73	85	97	100	103	109	121	124	127	133	145	148	151	169	+/- 1	
Informed consent	X																						
Urine drug/cotinine/alcohol test	X	X[r]																					
Virology test [a]	X																						
Demographics [b]	X	X																					
Medical and surgical history	X																						
Check In		X																					
Serum pregnancy test [c]		X																					
Apixaban [d]				X	X	X	X	X	X	X			X	X			X	X					
LT3001 drug product			X[t]							X	X	X		X	X	X		X	X	X			
Physical examination [e]	X		X						X											X		X	X
Vital sign [f]	X	X	X	X		X		X		X	X	X		X	X	X		X	X	X		X	X
12-lead ECG assessment [g]	X	X	X	X		X		X		X				X				X				X	X
LT3001PK blood sample			[redacted]																				
Apixaban PK blood sample [j]																							
Platelet function test		X[k]							X[k]	X[l]										X[m]		X	X
Coagulation [n]	X	X[r]							X[k]	X[l]										X[m]		X	X
Hematology test [o]	X	X[r]							X											X		X	X
Clinical chemistry test [p]	X	X[r]							X											X		X	X
Urinalysis [q]	X	X[r]							X											X		X	X
Discharge																					X		
Prior and concomitant medication	X	X	X																				
Adverse event	X	X	X																				

ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic

a. Virology tests will include HIV antibody, HBsAg, hepatitis C virus antibody, and COVID-19 antibody.

b. Demographics will include age, gender, height, body weight, BMI and race. On Day -1, only body weight will be measured.

c. Serum pregnancy test will be performed in female subjects of childbearing potential within 24 hours prior to the first drug treatment on Day 1.

d. The first dose of apixaban on Day 5, Day 6 and Day 7 will be followed immediately by 0.025 mg/kg LT3001 administered as a 15-minute IV infusion

e. Physical examination will be performed at screening visit, pre-dose on Day 1, the end of apixaban single treatment on Day 4, the end of combination treatment on Day 7 and follow-up visit on Day 14.

f. Vital signs will include body temperature, blood pressure, respiratory rate, and heart rate. Measurements will be made after the subject has rested in a supine position for at least 3 minutes. Blood pressure will be assessed in seated and supine position at predose and 60 minutes after dosing/infusion, only supine position at 20 minutes after dosing/infusion. Vital signs will be assessed at screening visit, Day 1 to 4 (pre-dose), Day 5 to Day 7 (each LT3001 dosing period at pre-dose, 20 minutes and 60 minutes after infusion is initiated) and follow-up visit on Day 14.

g. A 12-lead ECG assessment will be performed at screening visit and at pre-dose and 1 hour after taking Apixaban on Day 2 to Day 4, and after 1 hour after the infusion is initiated of the first dose of LT3001 on Day 5 o Day 7 and follow-up visit on Day 14.

h. PK blood samples of LT3001 will be co[redacted] 30±1, 45±1, and 60±5 minutes after inf

i. PK blood samples of LT3001 will be co[redacted] infusion is initiated (end of infusion).

j. PK blood samples of apixaban will be [redacted] PK samples of Day 4 and Day 7 will b[redacted] second dosing of apixaban on Day 5.)

k. Platelet function test and coagulation test will be measured at pre-dose on Day -1 and at 15 min and 6 hour15 min after the 2nd dose of apixaban on Day 4

l. Platelet function test and coagulation test will be measured on the first dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 5

m. Platelet function test and coagulation test will be measured on the last dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 7

n. Coagulation parameters will include PT, INR, aPTT and TT.

o. Hematology tests will include Hb, RBC, MCV, Hct, MCH, WBC, WBC-DC, and platelets.

p. Clinical chemistry tests will include BUN, creatinine, fasting blood glucose, ALP, ALT, AST, GGT, total bilirubin, total proteins, albumin/globulin ratio, Na, K, Cl, Ca, bicarbonate, uric acid, CK, cholesterol, triglycerides, free iron, and ferritin.

q. Urinalysis will include dipstick urinalysis and microscopic examination.

r. When the urine drug/cotinine/alcohol tests and/or clinical laboratory tests including coagulation, hematology and clinical chemistry are performed on Day -4 to Day -2, these tests need not be repeated on Day -1.

s. In the event of early termination (ET), a randomized subject will complete the ET procedures. The collection of PK blood samples of LT3001 and/or apixaban can be exempted based on the Investigator's discretion if the subject did not receive the indicated study drug.

t. A single dose of LT3001 drug product will be given on Day 1

u. A 30-minutes window is allowed for non-PK procedures.

Schedule of Activities for Part B, Cohort 4

Procedures	Screening Period		Treatment Period																		Follow-up	ET [s]
	Day -30 to -2	Day -1 Hour*	Day 1	Day 2		Day 3		Day 4		Day 5			Day 6				Day 7			Day 8	Day 14 +/- 1	
			1	25	37	49	61	73	85	97	100	103	109	121	124	127	133	145	148	151	169		
Informed consent	X																					
Urine drug/cotinine/alcohol test	X	X [r]																				
Virology test [a]	X																					
Demographics [b]	X	X																				
Medical and surgical history	X																					
Check In		X																				
Serum pregnancy test [c]		X																				
Dabigatran [d]				X	X	X	X	X	X	X			X	X			X	X				
LT3001 drug product			X[t]							X	X	X		X	X	X		X	X	X		
Physical examination [e]	X		X						X											X		X	X
Vital sign [f]	X	X	X	X		X		X		X	X	X		X	X	X		X	X	X		X	X
12-lead ECG assessment [g]	X	X	X	X		X		X		X				X				X				X	X
LT3001 PK blood sample			[redacted]																				
Dabigatran PK blood sample [j]																							
Platelet function test		X [k]							X [k]	X [l]										X [m]		X	X
Coagulation [n]	X	X [r]							X [k]	X [l]										X [m]		X	X
Hematology test [o]	X	X [r]							X											X		X	X
Clinical chemistry test [p]	X	X [r]							X											X		X	X
Urinalysis [q]	X	X [r]							X											X		X	X
Discharge																					X		
Prior and concomitant medication	X	X	X																				
Adverse event			X																				

ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic

a. Virology tests will include HIV antibody, HBsAg, hepatitis C virus antibody, and COVID-19 antibody.

b. Demographics will include age, gender, height, body weight, BMI and race. On Day -1, only body weight will be measured.

c. Serum pregnancy test will be performed in female subjects of childbearing potential within 24 hours prior to the first drug treatment on Day 1.

d. The first dose of dabigatran on Day 5, Day 6 and Day 7 will be followed immediately by 0.025 mg/kg LT3001 administered as a 15-minute IV infusion

e. Physical examination will be performed at screening visit, pre-dose on Day 1, the end of dabigatran single treatment on Day 4, the end of combination treatment on Day 7 and follow-up visit on Day 14.

f. Vital signs will include body temperature, blood pressure, respiratory rate, and heart rate. Measurements will be made after the subject has rested in a supine position for at least 3 minutes. Blood pressure will be assessed in seated and supine position at predose and 60 minutes after dosing/infusion, only supine position at 20 minutes after dosing/infusion. Vital signs will be assessed at screening visit, Day 1 to 4 (pre-dose), Day 5 to Day 7 (each LT3001 dosing period at pre-dose, 20 minutes and 60 minutes after infusion is initiated) and follow-up visit on Day 14.

g. A 12-lead ECG assessment will be performed at screening visit and at pre-dose and 1 hour after taking dabigatran on Day 2 to Day 4, and after 1 hour after the infusion is initiated of the first dose of LT3001 on Day 5 to Day 7 and follow-up visit on Day 14.

h. PK blood samples of LT3001 will be col[redacted] 45±1, and 60±5 minutes after infusion is

i. PK blood samples of LT3001 will be col[redacted] infusion is initiated (end of infusion).

j. PK blood samples of dabigatran will be [redacted] (The 24-hour PK samples of Day 4 and [redacted] prior to the second dosing of dabigatran [redacted]

k. Platelet function test and coagulation test will be measured at pre-dose on Day -1 and at 15 min and 6 hour15 min after the 2nd dose of dabigatran on Day 4

l. Platelet function test and coagulation test will be measured on the first dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 5

m. Platelet function test and coagulation test will be measured on the last dose of LT3001 at 15 min after infusion is initiated (end of infusion) on Day 7

n. Coagulation parameters will include PT, INR, aPTT and TT.

o. Hematology tests will include Hb, RBC, MCV, Hct, MCH, WBC, WBC-DC, and platelets.

p. Clinical chemistry tests will include BUN, creatinine, fasting blood glucose, ALP, ALT, AST, GGT, total bilirubin, total proteins, albumin/globulin ratio, Na, K, Cl, Ca, bicarbonate, uric acid, CK, cholesterol, triglycerides, free iron, and ferritin.

q. Urinalysis will include dipstick urinalysis and microscopic examination.

r. When the urine drug/cotinine/alcohol tests and/or clinical laboratory tests including coagulation, hematology and clinical chemistry are performed on Day -4 to Day -2, these tests need not be repeated on Day -1.

s. In the event of early termination (ET), a randomized subject will complete the ET procedures. The collection of PK blood samples of LT3001 and/or dabigatran can be exempted based on the Investigator's discretion if the subject did not receive the indicated study drug.

t. A single dose of LT3001 drug product will be given on Day 1.

u. A 30-minute window is allowed for non-PK procedures.

5. ANALYSIS SETS

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

Analysis Population	Description
Enrolled	All subjects who sign the ICF
Safety Analysis Set (SAS)	All subjects assigned to study treatment and who took at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they actually received.
Pharmacokinetic Analysis Set (PKAS)	All subjects assigned to study treatment, who took at least 1 dose of study treatment, and provided at least 1 PK sample. Subjects may be excluded from the PKAS on an individual basis, upon review of all records that have the potential to affect the PK data (e.g., dosing records, AEs, blooding sampling records, concomitant medications other than aspirin/clopidogrel/apixaban/dabigatran, protocol deviations of diet restriction).

6. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

6.1. Key Definitions

The Study Day is the day relative to the first day of study drug administration (Day 1).

Unless otherwise specified, Baseline is the last non-missing observation before the administration of any study treatment.

6.2. Visit Windows and Time Points

There are no plans to derive visit windows, and visits will be used in the analyses as reported on the eCRF.

6.3. Multiplicity Issues

For this early phase study, no multiplicity adjustment will be necessary as no hypothesis testing is being done.

6.4. Subgroup Analyses

Although no subgroup analyses are planned, Part A results will be presented by treatment (LT3001 and placebo) and population (Chinese and Non-Asian) and Part B results will be presented by cohort.

6.5. Missing Data

For prior and concomitant medication summaries, if the medication start date is completely missing then the medication will be considered both prior *and* concomitant unless it can be determined that the medication end date occurred prior to any study drug administration. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after study drug administration then the medication will be considered both prior *and* concomitant for the study unless the partial date is clearly after the date of first study drug administration (in which case it will be considered concomitant only) or the medication end date is prior to any study drug administration (in which case it is prior only).

Completely missing or partially missing adverse event onset dates will be imputed as follows in case due diligence to obtain accurate adverse event information fails:

- If the adverse event start date is completely missing then the adverse event will be considered treatment-emergent unless it can be determined that the adverse event end date occurred prior to administration of any study drug. If this is the case, the adverse event will not be considered treatment-emergent.
- If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the administration of any study drug, then the adverse event will be considered treatment-emergent unless it can be determined that the adverse event end date occurred prior to the start of the study.

No other missing data will be imputed.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

7.1. Subject Disposition and Populations

Summary tables for subject disposition will be presented for all enrolled subjects by Part and cohort. For Part A the disposition will be presented by treatment (LT3001 and placebo) and population ([redacted]), and for Part B the disposition will be presented by cohort. The subject disposition summary will contain the numbers of subjects who signed informed consent, failed screening, were randomized (Part A) or enrolled (Part B), completed that Part, and discontinued the study.

The primary reasons for premature discontinuation during the treatment periods will be summarized by Part and cohort for the SAS (Safety Analysis Set).

The number of subjects included in each analysis population will also be displayed.

Listings will also be presented on subject disposition and protocol violations.

7.2. Demographic and Baseline Characteristics

All subjects in the SAS will be used to summarize the demographic and baseline characteristics with respect to key variables such as age, sex, height, body weight, BMI, ethnicity and race. Summaries for other variables may be provided if needed.

Continuous variables will be summarized with descriptive statistics: n, mean, standard deviation, median, minimum, and maximum value. Categorical variables will be summarized with the number and percentages.

Other baseline characteristics such as COVID-19 screening, serum hcG pregnancy test, urine drug screen and alcohol breath test, and serology (HIV, HBV, HCV) screening will be listed for each subject.

A subject listing for demographic information will be provided by study part, cohort, and treatment (LT3001 or placebo).

7.3. Medical History

Medical history including existing diseases will be coded according to the latest version of the MedDRA dictionary. Frequency tables of the number and percentage of subjects by SOC (System Organ Class) and PT (Preferred Term) will be provided for the SAS.

Medical history will also be listed by subject.

7.4. Prior and Concomitant Medication

Medications will be separated into prior and concomitant medications. Prior medications are those with start and stop date before the first date of any study drug administration. Concomitant medications are those with either start date prior to the date of first study drug administration and were ongoing while for the duration of the study *or* those with start date after the date of first study drug administration. A medication can be considered both prior and concomitant.

All medications will be coded according to the latest version of the WHO Drug Dictionary and listed by subject. Prior and concomitant medications will be flagged accordingly. Concomitant medication will be summarized using the anatomical/therapeutic/chemical (ATC) code classification of drugs based on the WHO dictionary.

All medications will be listed. Prior and concomitant medications will be flagged accordingly.

The concomitant medications taken during Part B as part of the study design (aspirin, clopidogrel, apixaban or dabigatran) will not be included in these analyses.

7.5. Protocol Deviations

Protocol deviations and major protocol deviations are defined in the Clinical Monitoring Plan according to the ICH E3(R1) guidelines.

Protocol deviations are identified and recorded in the paper Protocol Deviation Log (PD Log) by the site staff. The clinical research associate (CRA) should review and ensure the deviations are accurately and completely recorded in the PD Log and signed by the investigator. Appropriate deviation category (i.e., major or minor) should be assigned as the table below.

Protocol Deviation Category	Major	Minor
Inclusion/Exclusion Criteria	X	
Informed Consent	X	
Enrollment: Enrolled but dosed incorrectly per cohort	X	
Randomization: Not randomized	X	
Investigation Product Dosing: Incorrect IP given to subject	X	
Investigation Product Dosing: IP dosing	X	
Out of Time Window Procedures		X
Study Procedure: Compliance		X
Study Procedure: Site Staff Authorization, Delegation, Training	X	
Blindness Failure	X	

All protocol deviations will be transferred from the completed PD log and finalized before the database lock.

Protocol deviations will be listed by subject.

8. PHARMACOKINETIC ANALYSIS

For PK analysis of LT3001 and concomitant medications (aspirin, clopidogrel, apixaban or dabigatran) blood samples will be collected throughout the treatment periods according to the PK sampling schedule in the Schedule of Activities (SoA) of the protocol and this SAP. All PK analysis will be based on the PKAS.

8.1. Handling of BLQ Values

To compute summary statistics for plasma concentration the BLQ plasma concentrations will be set to 0 for except for calculating geometric means and geometric CV%. For these two summary statistics it is set to LLOQ/2.

The BLQ values will be set to 0 in concentration-by-time linear plots and will be set to LLOQ/2 in concentration-by-time semi-logarithmic plots for mean and individual plots.

For calculation of the PK parameters, BLQ value(s) that occur at the beginning or at the end of serial sampling (before the first or after the last quantifiable concentration value, respectively) will be treated as zero. A BLQ value that is embedded between two quantifiable points will be treated as missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values may be excluded from the pharmacokinetic analysis by assigning them a value of missing unless otherwise warranted by the concentration-time profile.

8.2. Plasma PK: Part A

Plasma PK Concentration

Plasma concentrations of LT3001 will be summarized by population (Chinese vs. Non-Asian) with descriptive statistics: n, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum.

Plots of mean (SD) plasma concentration by time will be presented for LT3001 in linear and semi-logarithmic scales as well.

Plasma concentrations of LT3001 (Part A) at each nominal timepoint will be listed by subject.

Plasma PK Parameters

The following plasma PK parameters will be calculated for Part A for LT3001:

- C_{max}: Maximum (peak) plasma drug concentration during a dosing interval
- C_{min}: Trough plasma concentration
- C_{av}: Mean steady-state drug concentration
- t_{max}: Time to reach the observed maximum (peak) plasma concentration

- λ_z: Apparent first-order terminal elimination rate constant, calculated by linear least-squares regression analysis on the terminal log-linear phase of the plasma concentration vs time curves using at least 3 timepoints
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time zero to infinity, calculated as $AUC_{0-t} + C_t / \lambda_z$, where C_t is the last measurable concentration
- AUC_{0-t}: Area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
- $AUC_{0-\tau}$: Area under the plasma concentration-time curve over the dosing interval τ at steady-state
- R_{acc}: Accumulation ratio calculated as $AUC_{0-\tau,\ 1st\ dose}/AUC_{0-\tau,\ last\ dose}$ for the multi-day LT3001 regimens
- $MRT_{0-\infty}$: Mean residence time, calculated as $[AUMC_{0-\tau} + \tau(AUC_{0-\infty} - AUC_{0-\tau}]/AUC_{0-\tau} - (TI/2)$ where $AUMC_{0-\tau}$ is the area under the moment curve over dosing interval τ and TI represents infusion duration
- $t_{1/2,\lambda}$: Elimination half-life, calculated as $0.693 / \lambda_z$
- CL: Total body clearance of the drug from plasma, calculated as Dose / $AUC_{0-\infty}$
- V_z: Apparent volume of distribution during the terminal phase, calculated as (Dose / $AUC_{0-\infty}$ / λ_z
- V_{ss}: Apparent volume of distribution during steady state, calculated as CL x MRT

All calculations for plasma PK parameters will be based on actual dosing and sampling times recorded during the study. Plasma and urine pharmacokinetic parameters will be summarized (n, arithmetic mean, SD, CV%, minimum, median, and maximum) and listed by subject. Geometric mean (GM) and geometric CV% will also be presented for all AUC, C_{max}, C_{av}, and C_{min}.

Accumulation Ratio

To investigate whether the dose of LT3001 drug product is accumulated in the 3-day TID regimen, the potential dose accumulation effect will be assessed by comparing PK parameters of the first dose and the last dose in the multi-day TID regimen of LT3001 drug product.

Using a linear mixed-effects model with Race, Day (Day 1, first dose and Day 3, last dose), and Race-by-Day interaction as fixed effects, and subject as a random effect on log-transformed data, the geometric means and corresponding 95% CIs for AUC_{0-t}, $AUC_{0-\tau}$, and C_{max} will be presented for Chinese and Non-Asian subjects by exponentiating the model-based least-squared means. The geometric mean ratios (last dose/first dose) and the corresponding 90% CIs will also be calculated overall and for each race based on this model to assess accumulation.

8.3. Plasma PK: Part B

Plasma PK Concentration

Plasma concentrations of LT3001, aspirin (and metabolite salicylic acid), clopidogrel (and metabolite clopidogrel acid), apixaban, and dabigatran will be summarized by cohort with descriptive statistics: n, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum.

Plots of mean (SD) plasma concentration by time will be presented for LT3001 and concomitant medications by cohort in linear and semi-logarithmic scales as well.

Plasma concentrations of LT3001, concomitant medications, and metabolites for concomitant medications (Part B, Cohorts 1 and 2) at each nominal timepoint will be listed by subject.

Plasma PK Parameters

The following plasma PK parameters will be calculated for Part B for LT3001, concomitant medications, and metabolites for concomitant medications (Part B, Cohorts 1 and 2):

- C_{max}: Maximum (peak) plasma drug concentration during a dosing interval
- C_{min}: Trough plasma concentration
- C_{av}: Mean steady-state drug concentration
- t_{max}: Time to reach the observed maximum (peak) plasma concentration
- λ_z: Apparent first-order terminal elimination rate constant, calculated by linear least-squares regression analysis on the terminal log-linear phase of the plasma concentration vs time curves using at least 3 time points
- AUC_{0-t}: Area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
- $AUC_{0-\tau}$: Area under the plasma concentration-time curve over the dosing interval τ at steady-state
- R_{acc}: Accumulation ratio calculated as $AUC_{0-\tau,\ 1st\ dose}/AUC_{0-\tau,\ last\ dose}$ for the multi-day LT3001 regimens
- $MRT_{0-\infty}$: Mean residence time, calculated as $[AUMC_{0-\tau} + \tau(AUC_{0-\infty} - AUC_{0-\tau}]/AUC_{0-\tau} - (TI/2)$ where $AUMC_{0-\tau}$ is the area under the moment curve over dosing interval τ and TI represents infusion duration
- $t_{1/2,\lambda}$: Elimination half-life, calculated as $0.693 / \lambda_z$
- CL: Total body clearance of the drug from plasma, calculated as Dose / $AUC_{0-\tau}$

- V_z: Apparent volume of distribution during the terminal phase, calculated as (Dose / $AUC_{0-\tau}$ / λ_z

All calculations for PK parameters will be based on actual dosing and sampling times recorded during the study. Plasma and urine pharmacokinetic parameters will be summarized (n, arithmetic mean, SD, CV%, minimum, median, and maximum) and listed by subject. Geometric mean (GM) and geometric CV% will also be presented for all AUC, C_{max}, C_{av}, and C_{min}.

Accumulation Ratio

To investigate whether the dose of LT3001 drug product is accumulated in the multiday regimen, the potential dose accumulation effect will be assessed by comparing PK parameters of the first dose and the last dose in the multi-day TID regimen of LT3001 drug product. The comparisons will be conducted for occasions when LT3001 is alone or is coadministrated with aspirin, clopidogrel, apixaban, or dabigatran.

For each cohort based on a linear mixed-effects model with Day (Day of first dose and Day of last dose) as a fixed effect, and subject as a random effect on log-transformed data, the geometric means and corresponding 95% CIs for AUC_{0-t}, $AUC_{0-\tau}$, C_{max}, and C_{trough} will be presented by exponentiating the model-based least-squared means. The geometric mean ratios (last dose/first dose) and the corresponding 90% CIs will also be calculated for each cohort based on this model to assess accumulation.

Interaction with Aspirin

To assess the effect of aspirin on LT3001, a linear mixed-effects model with Day (Day 1 and Day 6) as a fixed effect, and subject as a random effect on log PK-parameters will be used to calculate 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of AUC_{0-t}, $AUC_{0-\tau}$, C_{max}, and C_{trough} by exponentiating the Least Square Mean Differences. The criteria of 90% CI within 50-200% of weak-effect boundaries will be used first for assessment. Only when the first criteria are satisfied, the second criteria of 90% CI within 80%-125% of no-effect boundaries will be used for further assessment.

The effect of LT3001 on the PK of aspirin will be assessed by comparing PK parameters of aspirin with and without LT3001 using a linear model similar to above with Day (Day 5 and Day 8) as fixed effect. PK parameters for comparison include $AUC_{(0-t)}$ and C_{max}.

Interaction with Clopidogrel

To assess the effect of clopidogrel on LT3001, a linear mixed-effects model with Day (Day 1 and Day 7) as a fixed effect, and subject as a random effect on log PK-parameters will be used to calculate 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of AUC_{0-t}, $AUC_{0-\tau}$, C_{max}, and C_{trough} by exponentiating the Least Square Mean Differences. The criteria of 90% CI within 50-200% of weak-effect boundaries will be used first for assessment. Only when the first criteria are satisfied, the second criteria of 90% CI within 80%-125% of no-effect boundaries will be used for further assessment.

The effect of LT3001 on the PK of clopidogrel will be assessed by comparing PK parameters of clopidogrel with and without LT3001 using a linear model similar to above with Day (Day 6 and Day 9) as fixed effect. PK parameters for comparison include $AUC_{(0-t)}$ and C_{max}.

Interaction with Apixaban

To assess the effect of apixaban on LT3001, a linear mixed-effects model with Day (Day 1 and Day 5) as a fixed effect, and subject as a random effect on log PK-parameters will be used to calculate 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of AUC_{0-t}, $AUC_{0-\tau}$, C_{max}, and C_{trough} by exponentiating the Least Square Mean Differences. The criteria of 90% CI within 50-200% of weak-effect boundaries will be used first for assessment. Only when the first criteria are satisfied, the second criteria of 90% CI within 80%-125% of no-effect boundaries will be used for further assessment.

The effect of LT3001 on the PK of apixaban will be assessed by comparing PK parameters of apixaban with and without LT3001 using a linear model similar to above with Day (Day 4 and Day 7) as fixed effect. PK parameters for comparison include $AUC_{(0-t)}$ and C_{max}.

Interaction with Dabigatran

To assess the effect of dabigatran on LT3001, a linear mixed-effects model with Day (Day 1 and Day 5) as a fixed effect, and subject as a random effect on log PK-parameters will be used to calculate 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of AUC_{0-t}, $AUC_{0-\tau}$, C_{max}, and C_{trough} by exponentiating the Least Square Mean Differences. The criteria of 90% CI within 50-200% of weak-effect boundaries will be used first for assessment. Only when the first criteria are satisfied, the second criteria of 90% CI within 80%-125% of no-effect boundaries will be used for further assessment.

The effect of LT3001 on the PK of dabigatran will be assessed by comparing PK parameters of dabigatran with and without LT3001 using a linear model similar to above with Day (Day 4 and Day 7) as fixed effect. PK parameters for comparison include $AUC_{(0-t)}$ and C_{max}.

8.4. Urine PK: Part A only

Urine PK Concentration

Urine concentrations of LT3001 and concomitant medications will be summarized with descriptive statistics (n, arithmetic mean, SD, CV%, minimum, median, and maximum) by treatment in Part and cohort and listed by subject.

Urine PK Parameters

The following urine PK parameters will be calculated for Part A:

- Ae_{x-y}: Amount of drug excreted in urine within a collection interval (x to y hours), where the values of x to y are 0 to 12 and 12 to 24
- Ae_{0-24}: Total amount of drug excreted in urine over the entire collection period (0 to 24 hours)
- Fe_{0-24}: Fraction excreted in urine from 0 to 24 hours after dosing, calculated as Ae_{0-24} / Dose × 100
- CL_R: Renal clearance, calculated as Ae_{0-24} / $AUC_{0-\infty}$

Urine PK parameters of LT3001 will be summarized with descriptive statistics (n, arithmetic mean, SD, CV%, minimum, median, and maximum) by treatment and listed by subject.

9. SAFETY ANALYSIS

Safety analyses will be performed on the SAS. Part A and Part B safety results will be presented separately. Part A data will be summarized by treatment and Part B data will be summarized by cohort.

9.1. Adverse Events

Adverse Events will be coded according to the latest version of the MedDRA dictionary. For this study, surveillance of adverse events (AE) will begin from Day 1 of the treatment period until the end of the follow-up or early termination.

Adverse events shall be recorded starting at signing of ICF. AEs will be defined as treatment-emergent adverse events (TEAE), if they occurred after administration of any study treatment or if they started prior to study drug administration but worsened after dosing, given that worsening started within the treatment period.

Only TEAEs shall be summarized in the clinical study report. An overall summary with number and percentage of subjects with all different TEAE categories, like treatment-related, serious, leading to withdrawal, and fatal will be provided. Incidence and severity of TEAEs will be summarized within System Organ Class (SOC), and within Preferred Term (PT).

TEAEs will be summarized by relationship per SOC and PT. Relationships will be categorized into related (includes "Related", "Possibly Related" and "Probably Related") and unrelated (includes "Not Related" and "Unlikely Related").

TEAEs will also be summarized by maximal severity per SOC and PT. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

All AEs will be listed by subject. Serious AEs (SAEs), TEAEs, and AEs leading to withdrawal will be flagged accordingly.

9.2. Clinical Laboratory Assessments

Clinical laboratory assessments including coagulation, platelet function test, hematology, clinical chemistry, and urinalyses will be summarized for each visit. In addition, changes from the baseline visit will be calculated for each visit if baseline and post-baseline measurements are available.

Shift tables will also be used to display the change from before treatment to after treatment measurement with respect to reference ranges "missing", "low", "normal", "high", and "total".

To investigate whether platelet function test is prolonged when coadminstrated with LT3001 drug product, platelet function test observed under single treatment of aspirin, clopidogrel, apixaban or dabigatran will be summarized along with coadministration with LT3001 drug product. The number of subjects with Prolonged and Normal results will be summarized for COL/EPI and COL/ADP.

All laboratory evaluations, including those that are unscheduled, will be listed by subject. Out of range and clinically significant (CS) values will be flagged.

9.3. Vital Signs

Vital signs, including the assessments of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature, will be summarized for each visit. In addition, changes from the baseline visit will be calculated for each visit.

All assessments, including those that are clinically significant (CS) or unscheduled, will be listed by subject.

9.4. ECG

ECG parameters, including heart rate, PR interval, QRS interval, QT interval, and QTc interval, will be summarized for each ECG parameter and visit. In addition, changes from the baseline visit will be calculated for each visit.

All assessments will be listed by subject, and abnormal or clinically significant (CS) findings will be flagged.

9.5. Pulse Oximetry

For Part A, pulse oximetry measurements will be summarized with descriptive statistics and listed by subject.

9.6. Physical Examination

For each body system, the number and percentage of subjects with normal and abnormal results will be presented. Additionally, changes in the subjects' findings from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be tabulated.

All physical examination findings, including those that are unscheduled, will be listed by subject and clinically significant (CS) findings will be flagged.

10. ANALYSIS CONVENTIONS

This section details general conventions to be used for the statistical analyses and presentation of results.

10.1. Analysis Convention:

- Summary statistics for continuous variables will include of sample size (n) mean, median, standard deviation (SD), minimum, and maximum values.
- Summary statistics for categorical variables will consist of the number and percentage of responses in each level.
- All study days, when displayed, are determined relative to the day of exposure to the treatment.
- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value.
- If there is imputation for missing data, the imputed or derived data are flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets (e.g., SDTM). The imputed data will be retained in the derived/analysis datasets (e.g., ADaM).
- SAS® Version 9.4 or higher will be the statistical software package used for all data analyses.

10.2. Display Convention:

- In post-text tables, figures and listings information and explanatory notes to be provided in the "footer" or bottom of each output will include the following information:

  1. Date and time of output generation
  2. SAS® program name
  3. Any other output specific details that require further elaboration.

- All summary tables will include the sample size for the Analysis Population as N in the column header.
- Supportive individual subject data listings will be sorted and presented by treatment/cohort, subject number, parameter and visit date/timepoint, if applicable.
- In general, tables will be formatted with a column displaying findings for all subjects. Missing statistics in the data summaries will be left blank (or a dash may be used as appropriate). Unknown ("NA"), not calculated ("NC"), or not reported ("NR") data are distinguished from missing data.
- In general, all mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal

places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. However, the precision may depend on specific measurements.

- PK concentrations will be displayed with the same precision as concentration data received from the bioanalytical lab. In descriptive statistics, calculations derived from PK concentrations (mean, SD, geometric mean, median, min, max) will follow the same precision. Coefficient of variations (CV%) will only be displayed with one decimal digit.
- For calculation of PK parameters, actual sampling times will be used with 3 decimal places. In general, 4 significant digits will be displayed for parameters such as AUC and Cmax, while t_{max} and $t_{1/2}$ will be displayed typically with 2 significant digits if the unit is expressed in hours, or if the unit is expressed in days sufficient significant digits to be able to convert back and identify the original sampling time. In descriptive statistics, (mean, min, max, median, SD etc.) will follow the same precision as the value of the parameter, coefficient of variations (CV%) will only be displayed with one decimal digit. Exceptions to the above can be made depending on sponsor feedback.
- The number and percentage of responses will be presented in the form XX (XX.X). Generally, only one decimal place will be used for the percentage. The % sign will be displayed on the column header. For 0 (0.0), only 0 will be displayed without the percentage.
- Row entries in tables are made only if data exists for at least one subject (i.e., unless requested, a row with all zeros will not appear). Exception to this rule applies to tables where all categories need to be shown (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied.
- For adverse event, the rows will be sorted to show the most frequent incidences showing first.
- Date and time variables will be formatted in ISO format (yyyy-mm-ddThh:mm) for presentation.
- In general, the study treatment, and subject number will be included in all data listings. All listings will be sorted by dose/cohort, subject number, parameter, visit, visit date, baseline severity, etc. as applicable.

11. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.
2. Certara USA, Inc. Phoenix® WinNonlin® Version 8.4 software, Princeton, NJ.

12. TABLES, LISTINGS, AND FIGURES

Tables, listings and figures will be listed in a separate Data Displays Document.

The outputs for Part A and Part B will be presented separately.