Title Page

Protocol 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

Protocol Number: LT3001-105

[redacted]

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Protocol Amendment Summary of Changes Table

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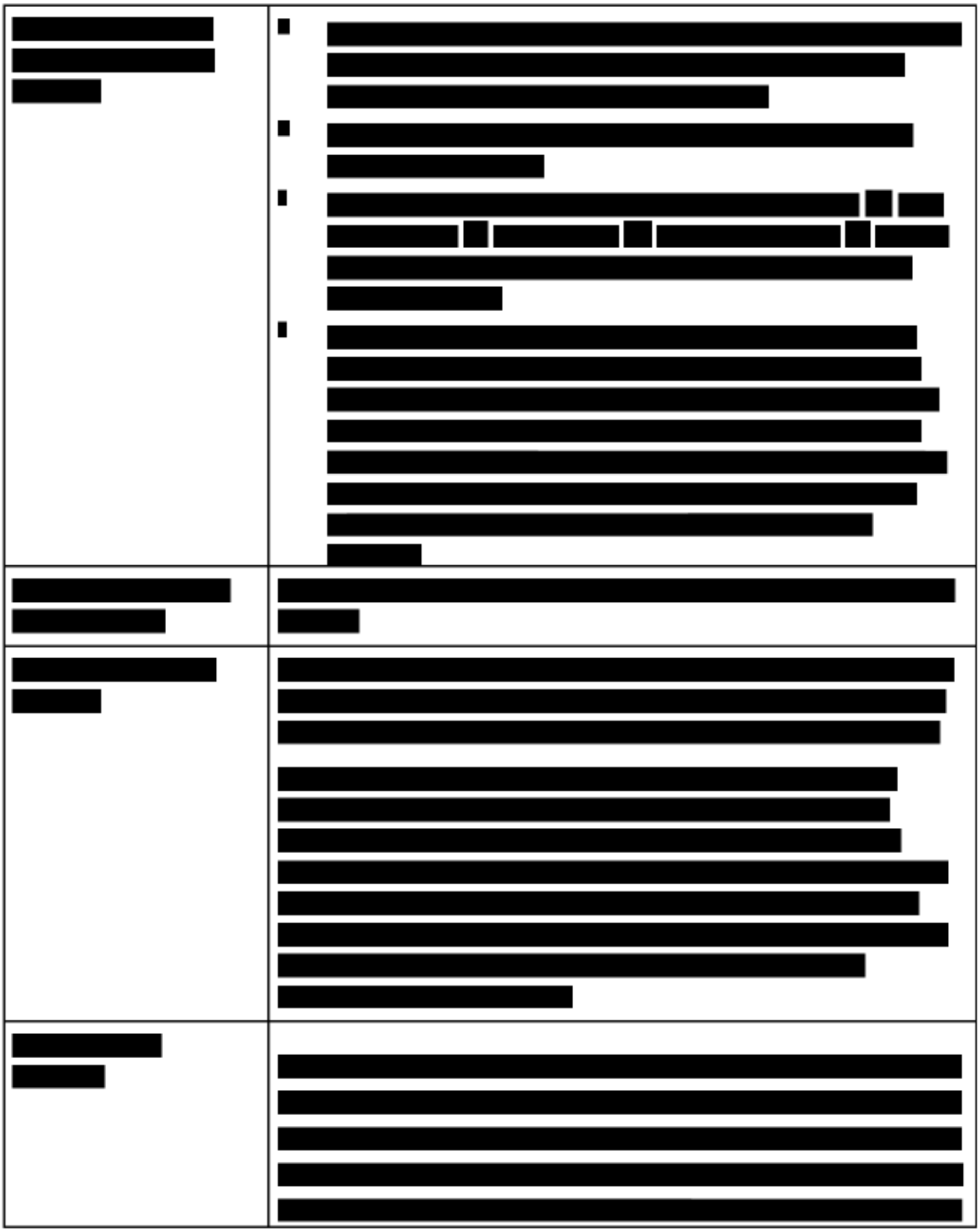

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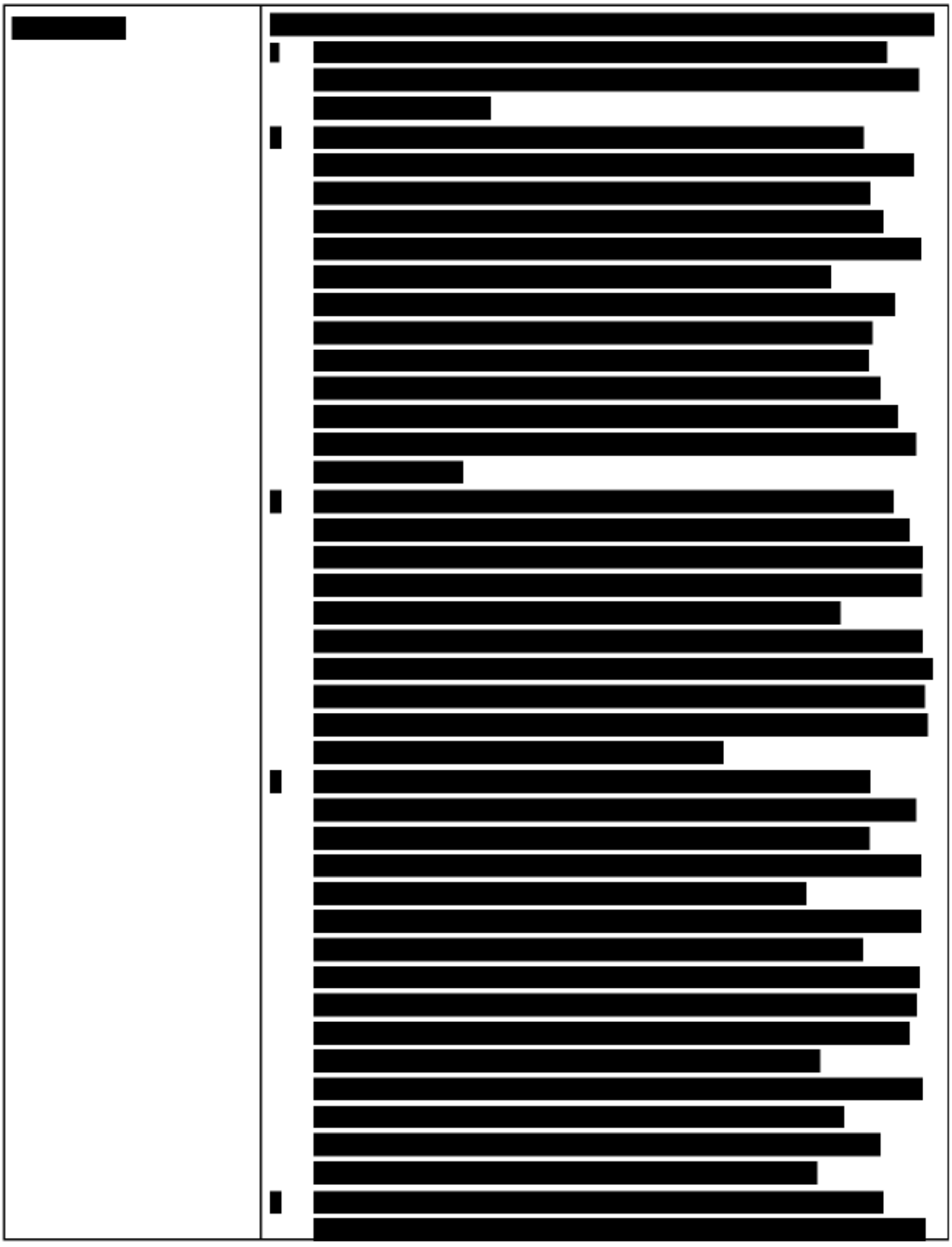

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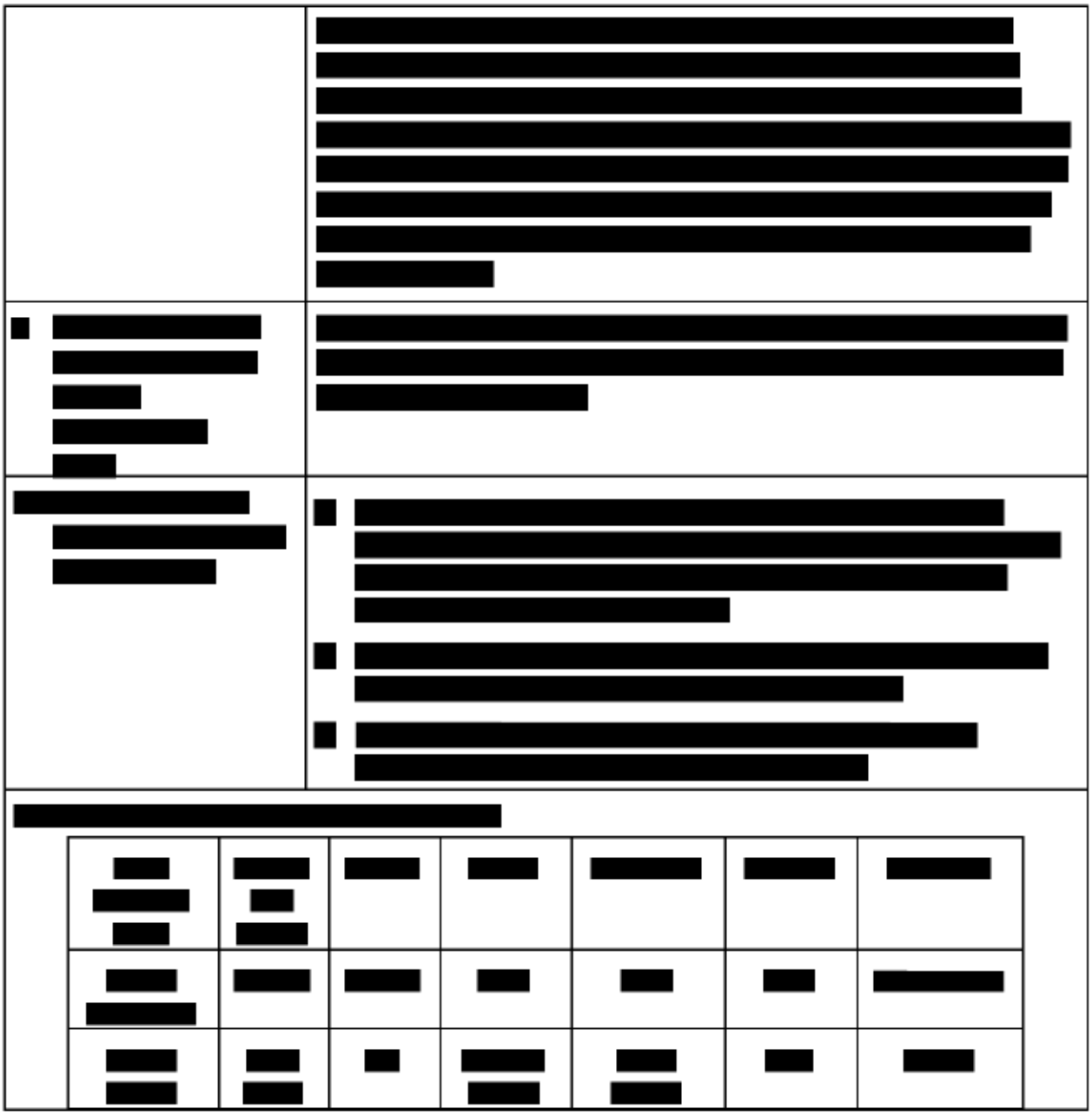

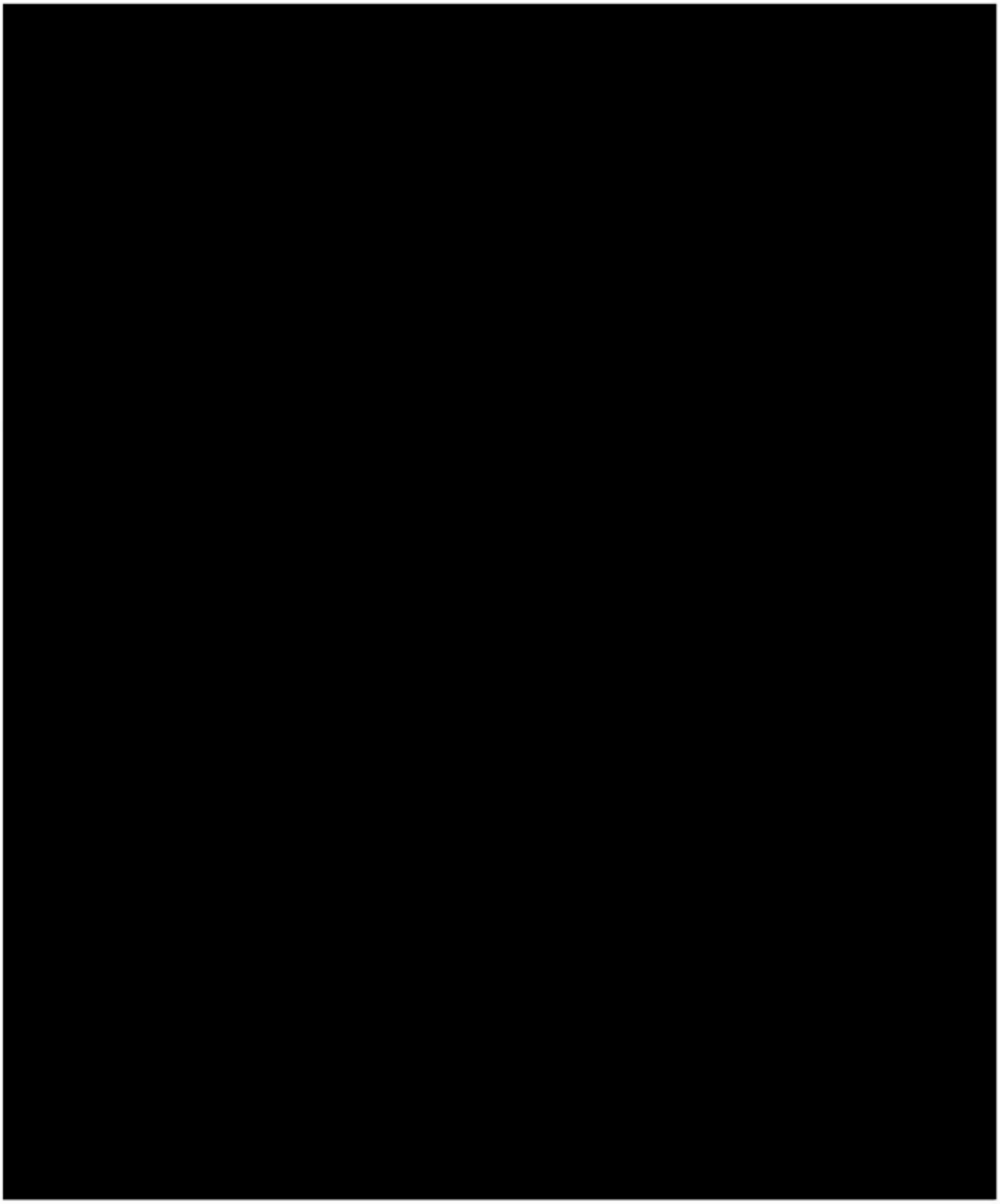

STUDY ADMINISTRATION

Study Role	Name, title, contact information
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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1. Synopsis

Protocol Title: A Double-Blind, Randomized, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Multiple Dose of LT3001 Drug Product and Drug-Drug Interaction in Healthy Adult Subjects

Short Title: a multiple dose and drug interaction study of LT3001 in healthy subjects

Rationale:

This Phase 1 study (LT3001-105) is planned to establish the clinical safety and pharmacokinetics (PK) profile of multiple dose of LT3001 drug product [redacted] and to investigate drug interactions of LT3001 with potential concomitant medications in healthy subjects.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A • To determine the safety, tolerability, and PK of a 3-day thrice daily (TID) use of LT3001 drug product, when administered as an IV infusion q3h between each dose within one day in healthy subjects (with half Chinese population).	Part A • 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)

Objectives	Endpoints
Primary	
Part B • To determine the safety and PK of LT3001 when coadministered with aspirin, clopidogrel, apixaban or dabigatran	Part B • Nature and severity of AEs and number of subjects with AEs • Changes from baseline in physical examination, vital signs, ECG assessment, platelet function test, oximetry, coagulation, and clinical laboratory tests. • Plasma PK parameters of LT3001 • Plasma PK parameters of aspirin, clopidogrel, apixaban, and dabigatran

Overall 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.

After provision of written informed consent, each subject will be evaluated for study eligibility during the screening period, which is within 30 days prior to receiving the study drug (Day 1).

Part A

Eligible subjects will be admitted to the site on Day -1 and undergo additional eligibility assessments. Those reconfirmed as eligible will be randomly assigned to study treatment. Approximately **16** healthy subjects will be randomized in a 3:1 ratio to receive either LT3001 drug product [redacted] 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. Subjects will be released from the site on Day 4 following all safety and PK procedures.

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.

The remaining subjects may not proceed to receive study drugs in the event of any of the following:

- A subject treated with LT3001 drug product experiences any hemorrhage which is assessed as related to LT3001 drug product
- A subject treated with LT3001 drug product experiences any serious AE (SAE) assessed as related to LT3001 drug product (at least possibly related)
- Safety concerns per the Investigator's clinical judgment

The dosing scheme is summarized below

[redacted]

The safety observation period may be extended beyond Day 4 in the event of any signal of significant clinical concern raised by the Investigator.

It will require approximately 5 weeks for each subject to complete all the required study procedures of Part A, including screening period, and blood samples will be collected from each subject for safety and PK evaluation during the study. Duration of both inpatient stay and PK sampling may be subject to change, depending on emerging safety and PK results.

After all healthy subjects complete study procedures of Part A, the safety review meeting will be held by the Investigator and the medical monitor 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

[redacted]

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.

The remaining combination treatments in a sentinel subject may not proceed in the event of any of the following:

- A subject experiences any severe hemorrhage which is assessed as related to the combination treatment
- A subject treated with LT3001 drug product experiences any SAE related to study drug (at least possibly related)
- Safety concerns per the Investigator's clinical judgment

The dosing schema is summarized below.

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 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. The regimen is intended to achieve its maximal inhibitory effects on platelet function. Aspirin will be administered after breakfast. On the morning of Day 6, the dose of aspirin will be followed by the first dose of LT3001 [redacted] administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 6 through 8 (three doses per day with three hours between doses). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 15.

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, a dosing paradigm consistent with clinical use in relevant indications. Clopidogrel will be administered after breakfast. On Day 7, the dose of clopidogrel will be followed by the first dose of LT3001 [redacted] administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 7 through 9 (three doses per day with three hours between doses). Each subject will be admitted into the study site on Day -1, stay until Day 10, and will have a follow-up visit on Day 16.

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. The morning doses of apixaban will be given after breakfast. 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 LT3001 [redacted] administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 5 to 7 (three doses per day with three hours between doses). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 14.

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. The morning doses of dabigatran will be given after breakfast. 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 LT3001 0.025 mg/kg administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 5 to 7 (three doses per day with three hours between doses). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 14.

Number of Participants:

Approximately 16 subjects [redacted] will be enrolled in Part A and 48 subjects in Part B.

Treatment Groups and Duration:

Part A: LT3001 or placebo, administered over 3 days

Part B:

Cohort 1: aspirin, with and without LT3001, over 7 days

Cohort 2: clopidogrel, with and without LT3001, over 8 days

Cohort 3: apixaban, with and without LT3001, over 6 days

Cohort 4: dabigatran, with and without LT3001, over 6 days

Total study duration is expected to be 3 months.

Investigational Product (IP), Dose, and Mode of Administration

LT3001, [redacted]

Placebo, administered as a [redacted]

Non-IP Study Medications/Reference Products, Dose, and Mode of Administration

Aspirin, [redacted]

Clopidogrel, [redacted]

Apixaban, [redacted]

Dabigatran, [redacted]

Statistical Methods

Sample Size Determination:

There were no statistical considerations in determining sample size. Twelve to 16 subjects per treatment group is deemed to be sufficient to meet the study objectives.

Safety Analysis:

[redacted]

Pharmacokinetic Analysis:

From the **plasma** concentration-time data, the following PK parameters will be determined, as data permit:

C_{max}	Maximum plasma 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) 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
$AUC_{0-\infty}$	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

$AUC_{0\text{-}tau}$	AUC over the dosing interval τ at steady-state
$MRT_{0\text{-}\infty}$	Mean residence time, calculated as $\frac{AUMC_{0-\tau} + \tau(AUC_{0-\infty} - AUC_{0-\tau})}{AUC_{0-\tau}} - \frac{TI}{2}$ where $AUMC_{0\text{-}\tau}$ is the area under the moment curve over dosing interval τ, TI represents infusion duration.
$t_{1/2}$	Elimination half-life, calculated as $0.693 / \lambda_z$
CL	Total body clearance of the drug from plasma, calculated as Dose / $AUC_{0\text{-}\infty}$
V_z	Apparent volume of distribution during the terminal phase, calculated as (Dose / $AUC_{0\text{-}\infty}$) / λ_z
V_{ss}	Apparent volume of distribution during steady state, calculated as CL × MRT

[redacted]

From the **urine** concentration data, the following PK parameters will be determined, as data permit:

$Ae_{x\text{-}y}$	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
$Ae_{0\text{-}24}$	Total amount of drug excreted in urine over the entire collection period (0 to 24 hours)
$Fe_{0\text{-}24}$	Fraction excreted in urine from 0 to 24 hours after dosing, calculated as $Ae_{0\text{-}24}$ / Dose × 100
CLr	Renal clearance, calculated as $Ae_{0\text{-}24}$ / $AUC_{0\text{-}\infty}$

Urine PK parameters will be listed by subject and treatment and summarized by treatment using the PKAS and the following summary statistics: n, arithmetic mean, SD, CV, minimum, median, and maximum.

Pharmacokinetic/Safety Analyses

Pharmacokinetic and safety parameters of special interest will be assessed descriptively whenever possible and by exploratory statistical comparisons and required plots of the potential PK-safety relationship between LT3001 levels in plasma and all applicable safety parameters (absolute and/or baseline adjusted) will be presented.

Drug/Drug Interactions

The effect of aspirin, clopidogrel, apixaban or dabigatran on the PK of LT3001 as well as the effect of LT3001 on the PK of aspirin, clopidogrel, apixaban or dabigatran will be assessed by comparing steady-state PK parameters of LT3001 and these concomitant medications.

2. Schedule of Activities (SoA)

Table 1 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[n]			X[n]	X[n]			X[n]	X[n]			X[n]	X[n]
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 [redacted]

[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 [redacted]

[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 [redacted]

[m] PK blood samples will be collected [redacted]

n. PK urine samples will be [redacted]

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.

Table 2 Schedule of Activities for Part B, Cohort 1

Procedures	Screening Period		Treatment Period														Follow-up	ET [s]
	Day -30 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6			Day 7			Day 8			Day 15	
		Hour [n]	1	25	49	73	97	121	124	127	145	148	151	169	172	175	+/- 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																
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 [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, 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 [redacted] 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, 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 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 visi[redacted]

[h] PK blood samples of LT3001 will be collected[redacted]

[i] PK blood samples of LT3001 will be collec[redacted]

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

[k] Platelet function test and coagulation test will be measured[redacted]

[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

Table 3 Schedule of Activities for Part B, Cohort 2

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 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[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	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 [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																	
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 [redacted] 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 [redacted].

[i] PK blood samples of LT3001 will be collected on [redacted]

[j] PK blood samples of clopidogrel will be [redacted]

[k] Platelet function test and coagulation test will be measured [redacted]

[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.

Table 4 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[n]	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 [redacted] 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 [redacted].

[h] PK blood samples of LT3001 will be collected [redacted].

[i] PK blood samples of LT3001 will be collected [redacted]).

[j] PK blood samples of apixaban will be [redacted].

[k] Platelet function test and coagulation test will be [redacted]

[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.

Table 5 Schedule of Activities for Part B, Cohort 4

Procedures	Screening Period		Treatment Period																		Follow-up	ET [s]
	Day -30 to -2	Day -1 Hour[n]	Day 1 1	Day 2 25	Day 2 37	Day 3 49	Day 3 61	Day 4 73	Day 4 85	Day 5 97	Day 5 100	Day 5 103	Day 5 109	Day 6 121	Day 6 124	Day 6 127	Day 6 133	Day 7 145	Day 7 148	Day 7 151	Day 8 169	Day 14 +/- 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																					
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																							
Dabigatran PK blood sample [j]																							
Platelet function test																							
Coagulation [n]	X	X [r]							X [k]	X [l]										X		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 [redacted] 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 [redacted]

[h] PK blood samples of LT3001 will be [redacted]

[i] PK blood samples of LT3001 will be [redacted]

[j] PK blood samples of dabigatran will be collected [redacted].

[k] Platelet function test and coagulation test will be [redacted]

[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.

3. Introduction

3.1. Study Rationale

This Phase 1 study (LT3001-105) is planned to establish the clinical safety and pharmacokinetics (PK) profile of multiple dose of LT3001 drug product [redacted] and to investigate drug interactions of LT3001 with potential concomitant medications in healthy subjects.

3.2. Background

[redacted]

LT3001 is a novel small molecule with both cerebral blood flow restoration and free radical-scavenging activities as shown in nonclinical studies and thus can potentially be a new therapy for treating acute ischemic stroke.

A Phase 1 single IV infusion of LT3001 drug product in health volunteer study (LT3001-101) has been completed at a clinical site in the United States, which indicate that the LT3001 drug product is safe and well tolerated at all doses tested (single dose of [redacted] given as a 15 minute IV infusion).

The safety of LT3001 with concomitant drugs commonly used by acute ischemic stroke patients is therefore of great interest. Antiplatelet agents, such as aspirin and clopidogrel, are used for both the management of acute ischemic stroke and the prevention of stroke. Anticoagulants including apixaban and dabigatran are commonly used for stroke prevention in atrial fibrillation patients.

3.2.1. Nonclinical Studies

LT3001 is a novel small molecule designed to have both thrombolytic and free radical-scavenging activities, which were characterized in various in vitro and in vivo models. In vitro studies have shown that LT3001 exhibited substantial antioxidation activity. In animal studies LT3001 can restore blood flow, reduce cerebral infarct volume, and improve neurological outcome in rodent and nonhuman primate stroke models, with an apparent wider therapeutic time window and a better safety profile than those reported for rtPA. The effect of LT3001 on the bleeding time was evaluated in male ICR mice and was comparable to animals that received vehicle control and significantly shorter than those treated with rtPA (10 mg/kg).

[redacted]

[redacted]

[redacted]

[redacted]

3.2.2. Clinical Studies

[redacted]

[redacted]

[redacted]

[redacted]

3.2.3. Safety

Clinical evidence in healthy subjects indicate that the LT3001 drug product is safe and well-tolerated at the doses tested (ie, single doses of [redacted] given as a 15-minute IV infusion).

3.3. Benefit/Risk Assessment

The dose selected for this multiple-dose study had been previously evaluated in a single dose study. There were no clinically significant changes in safety parameters. No clinical efficacy studies have been completed with LT3001 Drug Product, so a direct benefit-risk assessment has not been performed.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LT3001 may be found in the Investigator's Brochure.

4. Objectives and Endpoints

Objectives	Endpoints
Primary	
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 half Chinese population).	Part A • 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 • To determine the safety and PK of LT3001 when coadministered with aspirin, clopidogrel, apixaban or dabigatran	Part B • Nature and severity of AEs and number of subjects with AEs • Changes from baseline in physical examination, vital signs, ECG assessment, oximetry, platelet function test, coagulation, and clinical laboratory tests. • Plasma PK parameters of LT3001 • Plasma PK parameters of aspirin, clopidogrel, apixaban and dabigatran

5. Study Design

5.1. Overall Design

This study is a two-part study (Figure 1). 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.

After provision of written informed consent, each subject will be evaluated for study eligibility during the screening period, which is within 30 days prior to receiving the study drug (Day 1).

Part A

Eligible subjects will be admitted to the site on Day -1 and undergo additional eligibility assessments. Those reconfirmed as eligible will be randomly assigned to study treatment. Approximately **16** healthy subjects will be randomized in a3:1 ratio to receive either LT3001 drug product [redacted] 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. Subjects will be released from the site on Day 4 following all safety and PK procedures.

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.

The remaining subjects may not proceed to receive study drugs in the event of any of the following:

- A subject treated with LT3001 drug product experiences any hemorrhage which is assessed as related to LT3001 drug product
- A subject treated with LT3001 drug product experiences any SAE is assessed as related to LT3001 drug product (at least possibly related)
- Safety concerns per the Investigator's clinical judgment

The dosing schema is summarized below.

[redacted]

The safety observation period may be extended beyond Day 4 in the event of any signal of significant clinical concern raised by the Investigator.

It will require approximately 5 weeks for each subject to complete all the required study procedures of Part A, including screening period, and blood samples will be collected from each subject for safety and PK evaluation during the study. Duration of both inpatient stay and PK sampling may be subject to change, depending on emerging safety and PK results.

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

Safety Review Schema

[redacted]

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.

The remaining combination treatments in a sentinel subject may not proceed in the event of any of the following:

- A subject experiences any severe hemorrhage which is assessed as related to the combination treatment
- A subject treated with LT3001 drug product experiences any SAE related to study drug (at least possibly related)
- Safety concerns per the Investigator's clinical judgment

The dosing schema is summarized below.

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 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 (Figure 2). The regimen is intended to achieve its maximal inhibitory effects on platelet function. Aspirin will be administered after breakfast. On the morning of Day 6, the dose of aspirin will be followed by the first dose of LT3001 0.025 mg/kg administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 6 through 8 (TID q3h). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 15.

Figure 2 Dosing Schema of LT3001 and Aspirin Co-administration

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, a dosing paradigm consistent with clinical use in relevant indications (Figure 3). Clopidogrel will be administered after breakfast. On Day 7, the dose of clopidogrel will be followed by the first dose of LT3001 [redacted] administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 7 through 9 (TID q3h). Each subject will be admitted into the study site on Day -1, stay until Day 10, and will have a follow-up visit on Day 16.

Figure 3 Dosing Schema of LT3001 and Clopidogrel Co-administration

In **Cohort 3**, each subject will receive a single 15-minute infusion of LT3001 [redacted] 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 (Figure 4). The morning doses of apixaban will be administered after breakfast. 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 LT3001 0.025 mg/kg administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 5 to 7 (TID q3h). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 14.

Figure 4 Dosing Schema of LT3001 and Apixaban Co-administration

In **Cohort 4**, each subject will receive a single 15-minute infusion of LT3001 [redacted] Day 1. Each subject will receive multiple-dose dabigatran as follows: 110 mg dabigatran BID (q12h) on Days 2 through 7 (Figure 5). The morning doses of dabigatran will be administered after breakfast. 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 LT3001 0.025 mg/kg administered as a 15-minute IV infusion. Subjects will receive 9 doses of LT3001 on Days 5 to

7 (TID q3h). Each subject will be admitted into the study site on Day -1, stay until Day 8, and will have a follow-up visit on Day 14.

Figure 5 Dosing Schema of LT3001 and Dabigatran Co-administration

5.2. Participant and Study Completion

Approximately 16 subjects (8 Chinese and 8 non-Asian) will be enrolled in Part A and 48 subjects in Part B. A subject will have completed the study when the final PK and safety assessments are done at the end-of-study (EOS) or follow-up visit.

5.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

Studies comparing the PK and safety of a drug product in Chinese and non-Asian subjects allow for extrapolation of clinical data across regions. Use of healthy participants rather than patients minimizes confounding factors due to disease. Randomization and blinding minimizes bias in the assessment of safety and interpretation of results. The susceptibility of LT3001 to drug interaction will be assessed by measuring LT3001 when administered alone and in combination with aspirin, apixaban, clopidogrel, and dabigatran. Similarly, the effect of LT3001 on aspirin, apixaban, clopidogrel, and dabigatran will be assessed by measuring those analytes alone and in combination with LT3001.

5.5. Justification for Dose

. There were no clinically significant changes in safety parameters and AUC was within the predetermined bounds.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Signed the informed consent form (ICF) as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF (ICF) and in this protocol
2. Subject is a male or female between 18 and 65 years of age on the day of screening.
3. Subject's body weight is ≥50 kg and body mass index is within the range of 18 to 32 kg/m2 (inclusive).
4. Subject is a healthy volunteer confirmed by a comprehensive clinical assessment, including detailed medical history, a complete physical examination, fasting blood glucose, vital sign measurements, ECG results, and laboratory investigations (hematology, clinical chemistry, and urinalysis). The results should be clinically acceptable for healthy subjects per the principle Investigator's assessment.
5. Subject's PT, aPTT, and TT are within the normal laboratory range.
6. Female subject must be of non-childbearing potential or, if of child-bearing potential, must be using medically acceptable contraceptive measures (Appendix 5) throughout the duration of the study and for at least 30 days after receiving the last dose of study treatment. A woman of nonchildbearing potential is defined as a woman who is over 55 years old and postmenopausal at least 12 months prior to screening or a woman who is surgically sterile.
7. Male subjects and their partners of childbearing potential must commit to the use of medically acceptable contraception (Appendix 5) for the study duration. Men must refrain from donating sperm during this same period. The female partners should be asked to use a contraception method that is medically acceptable, and these contraceptive measures should be used throughout the duration of the study and for at least 30 days after their last dose of study treatment.
8. Subject is a nonsmoker (abstinence for at least 6 months prior to screening).
9. A Chinese subject is defined as a first-generation Chinese (both parents of Chinese descent) who maintains a typical Chinese lifestyle, including diet. In addition to mainland China, subjects or their parents may also be from Taiwan, Hong Kong, or Mongolia.

Note: Retesting of abnormal lab values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Subject has a positive result from an alcohol or drug test for amphetamines, barbiturates, cocaine, opiates, cannabinoids, or benzodiazepines during screening.
2. Subject has a positive result from a hepatitis B virus (HBV) test (hepatitis B surface antigen; HBsAg) or hepatitis C virus (HCV) test (anti-HCV antibody) within 3 months of screening.
3. Subject has a history of HIV infection.
4. Subject has a current or recent history (within 6 months prior to screening) of regular alcohol consumption (ie, at least 2 ounces of alcohol or 2 drinks per day).
5. Subject has received any investigational product within 30 days or 5 half-lives (whichever is longer) prior to the first dosing day or is planning to participate in a clinical trial during the study period.
6. Subject has used prescription or nonprescription drugs, including vitamins, herbal and dietary supplements within 7 days prior to the first dose of study drug, unless the medication will not interfere with the study procedures or compromise subject safety in the opinion of the Investigator.
7. Subject has a history of sensitivity to any of the study drugs or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator, contraindicates participation.
8. Subject has donated blood or blood products within 56 days prior to screening.
9. Female subject of childbearing potential has a positive result for serum pregnancy test on Day -1.
10. Male subject is planning a pregnancy with a female partner from screening until 30 days after completing study drug treatment.
11. Subject is unwilling or unable to follow the procedures outlined in the protocol in the opinion of the Investigator.
12. Subject has a presence or history of coagulation abnormality.
13. Subject has abnormal laboratory values or clinical findings on screening that are judged clinically significant by the Investigator.
14. Subject has a history of clinically significant renal or liver dysfunction.
15. Subject has a presence or history of psychiatric illness or mental impairment.
16. Subject has a significant risk for suicidal behavior in the opinion of the Investigator.
17. Subject has a history of long QT syndrome (personal or family) or cardiac conduction disorder, or clinically significant cardiac disease.
18. Urinary cotinine levels at screening are indicative of smoking or subject has history of regular use of tobacco- or nicotine-containing products prior to screening.
19. Subject is an employee (permanent, temporary contract worker, or designee responsible for the conduct of the study) of the Investigator or study site, or immediate family* of such employees or the Investigator.
20. Subject is an employee or immediate family* of an employee of Lumosa Therapeutics Co., Ltd. or contract research organization conducting the trial.

    (*Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.)

21. Subject has an active infection of coronavirus disease 2019 at screening.

22. Subjects who are enrolled in Part B and allergic to acetylsalicylic acid, other salicylates, clopidogrel, thienopyridines (eg, ticlopidine, prasugrel), apixaban or dabigatran.
23. Subjects who are enrolled in Part B and taking medications that affect the PK characteristics of aspirin, clopidogrel, apixaban or dabigatran.
24. Subjects need to receive a surgery or clinical procedures associated with high bleeding risk.
25. Part B Cohort 2 only: subjects who are poor metabolizers of clopidogrel (CYP2C19*2/*2, *2/*3, or *3/*3 genotype)
26. Subject has a history of minor bleeding episodes, eg, epistaxis, rectal bleeding, gingival bleeding.
27. Subject has a history of peptic ulcer or gastrointestinal bleeding.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

1. Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 3 days before the start of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

1. Subjects will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before collection of any PK sample until after collection of the final PK sample.
2. Subjects will abstain from alcohol for 24 hours before the first dose until after collection of the final PK sample.
3. Use of tobacco products will not be allowed during the study.

6.3.3. Activity

1. Subjects will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Table 6 Identity of Study Treatments

Study Treatment Name	LT3001 drug product	Placebo	Aspirin	Clopidogrel	Apixaban	Dabigatran
Dosage formulation	solution	solution	tablet	tablet	tablet	capsule
Dosage level(s)	[redacted]					
Route of Administration	IV infusion	IV infusion	Oral	Oral	Oral	Oral
Dosing instructions Part A	15 minute infusion TID q3h for 3 days		NA	NA	NA	NA
Dosing instructions Part B	[redacted]					
Packaging and Labeling	Study Treatment will be provided in a vial. Each vial will be labeled as required per country requirement.		Commercial packaging			
Manufacturer	[redacted]					

7.2. LT3001 Drug Product and Placebo

LT3001 drug product will be provided as a preservative-free, sterile, lyophilized powder for injection in glass vials with butyl rubber stoppers and flip-off aluminum crimp seals. Each vial will contain LT3001 drug substance, equivalent to 20 mg free base, as a white to off-white lyophilized cake or powder. Placebo is formulated identically in the components, composition, and appearance to LT3001 drug product but does not contain the active compound. The LT3001 drug product should be stored at 2°C to 8°C (35.6°F to 46.4°F).

The dose level of LT3001 drug product will be calculated by the Investigator or a qualified designee based on the subject's body weight and confirmed by the unblinded pharmacist before study treatment preparation.

LT3001 drug product and placebo should be reconstituted prior to use with normal saline (0.9% Sodium Chloride) to a final concentration of 4 mg/mL. LT3001 drug product will be further diluted to a suitable concentration with normal saline and administered via a 15-minute IV infusion. Instructions for reconstitution and dilution will be provided separately to the sites.

The reconstituted LT3001 drug product and placebo solution could be stored at room temperature for 8 hours or at 2°C to 8°C (35.6°F to 46.4°F) for 24 hours.

Drug supplies of LT3001 drug product and placebo will be provided by the Sponsor.

7.3. Dose Modification

No changes to doses or dosing schedule are allowed.

7.4. Method of Treatment Assignment

In Part A, the first four sentinel subjects will be randomly assigned to LT3001 drug product or placebo in a 1:1 ratio. The remaining subjects will be randomized in a 3:1 ratio.

In Part B, subjects will be sequentially assigned to one of four treatment cohorts.

7.5. Randomization Procedures

In Part A, in order to preserve the blinding of the subject or the personnel involved in subject evaluations or data collection, an unblinded pharmacist who is not directly involved in the study conduct, data management, or data analysis will be designated. The Investigator or designee should provide the necessary information to the unblinded pharmacist who will obtain the assignment of the subject's treatment according to the randomization code list. Neither the subject nor the Investigator will know the treatment to which the subject has been assigned.

7.6. Maintenance of Randomization Codes

In Part A, randomization codes will be provided to the unblinded pharmacist who prepares study treatments and the unblinded biostatistician(s) perform the PK analysis at the beginning of Part A. The pharmacist will use the randomization code list for treatment assignment and preparing subject doses throughout the study.

7.7. Blinding

Part A is double-blind. The unblinded pharmacist at the study site will prepare the study drug. In order to protect the blinding of the subjects and Investigators, the IV bag will be masked properly. Because of the double-blind design of Part A, the Investigator or designee should treat and evaluate all subjects as though they received LT3001 drug product. Only the pharmacist responsible for treatment

assignment and the biostatisticians generating the randomization code or performing the unblinded PK analyses will be unblinded and will have access to treatment assignments; all other parties involved in the study will be fully blinded until Part A is completed.

For the safety review meeting of Part A, a blinded PK analysis will be conducted after all healthy subjects complete study procedures of Part A and blood PK data will be reviewed in a blind manner in the meeting.

Part B is open-label.

7.8. Breaking the Blind

A subject's treatment assignment will not be broken until the end of Part A unless, in the Investigator's opinion, knowledge of treatment assignment would alter management of SAEs or non-serious AE of Grade 3 or higher severity. In the event that the blind needs to be broken because of a medical emergency, the Investigator may be unblinded to obtain the subject's treatment assignment. Prior to unblinding a subject's treatment assignment, the Investigator should make every effort to contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. If a subject's treatment is unblinded, Lumosa must be notified immediately. The Investigator or designee must clearly document any unblinding event and the documentation must include the subject number, the reasons for treatment unblinding, and the date on which the code was broken.

7.9. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator will maintain accurate records of drug disposition required by applicable law, including date and quality administered, and subject to whom study drug was administered. Reasons for departure from the expected dispensing regimen must also be recorded.

A study drug accountability log will be used to document study drug disposition. All items on the log are to be completed in full. The study clinical research associate will ensure that the area where the study drug accountability records are to be maintained is adequate.

Each time the pharmacist designated by the Investigator dispenses study drug for a subject, he or she is to record the subject number and initials, randomization number, date dispensed, number of vials of study drug dispensed, and his or her initials. The study clinical research associate will count all used and unused containers of study drug and review study drug accountability records during routine monitoring visits. The clinical research associate will also need to verify dose calculation to check whether the actual doses administered were the same as those intended.

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, the amount of study drug will be reconciled and retained on site, the unused study drug will be arranged for return to the sponsor, or destruction according to site's standard protocols.

7.10. Treatment Compliance

LT3001 drug product will be administered via an IV infusion by the Investigator or qualified personnel.

Aspirin, clopidogrel, dabigatran, and apixaban will be orally administered under the direct supervision of the Investigator or designee. A hand and mouth check will be done to ensure that the medication was swallowed.

7.11. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Except as note below, subjects must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and sponsor, the medication will not interfere with the study. In particular, any medication which affects blood pressure or coagulation functions is prohibited.

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use at any time during the study. Oral contraceptives and hormone replacement therapy are also allowed. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

7.11.1. Rescue Medicine

There is no rescue medication for this study.

7.12. Treatment after the End of the Study

Subjects will not receive study medication after the end of the study.

8. Discontinuation/Withdrawal Criteria

8.1. Discontinuation of Study Treatment

If a clinically significant AE is identified after enrollment, the Investigator or Medical Monitor will determine if the subject can continue in the study and if any change in subject management is needed.

In Part A, dosing of an individual subject will be discontinued in the event of the following:

- Clinically significant changes in coagulation parameters, which indicate that hemorrhage might occur.
- Subject experiences an AE of Grade 3 or higher severity
- Investigator or designee determines that discontinuation of dosing is in the best interest of the subject

In Part B, dosing of an individual subject will be discontinued in the event of the following:

- Subject experiences an AE of Grade 3 or higher severity
- Investigator or designee determines that discontinuation of dosing is in the best interest of the subject

Part A and each cohort of Part B will be terminated when two subjects within the same cohort experience any study drug related SAE or non-serious AE of Grade 3 or higher severity (at least possibly related).

See the Schedule of Activitie (SoA, Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.1. Temporary Discontinuation

If a non-serious AE which resulted in discontinuation resolves without sequelae, the Investigator may allow the subject to re-join the study within the same cohort.

8.1.2. Rechallenge

Subjects who temporarily discontinued study treatment due to a non-serious AE will be closely monitored during rechallenge. A recurrence of the original AE, or a worsening of the AE, will result in permanent discontinuation of that subject from the study.

8.2. Withdrawal from the Study

The study inclusion and exclusion criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject shall be withdrawn from the study.

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

Additionally, this study may be terminated at the discretion of the Sponsor. The Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP).

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All the enrolled subjects withdrawn from the study are encouraged to complete all end-of-study (EOS) or early termination (ET) assessments.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator in the subject's source documents and on the relevant page of the electronic case report form (eCRF).

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.4. Replacements

If a subject is withdrawn from the treatment period of the study for reasons not associated with LT3001 drug product-related safety considerations, the subject will be replaced with another subject assigned to the same treatment with respect to LT3001 drug product and placebo doses (Part A) or a specific cohort (Part B). Subjects who are replacements will be allocated the same randomization number with the first digit of treatment number being replaced by the number 1 (eg, if randomization number R01001 is replaced, then the replacement number will be R01101).

9. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 2). Total volume of blood per subject in each cohort summarized in the Table 7.

Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Table 7 Total Volume of Blood Per Subject in Each Cohort

Type of Sample	**Volume per Sample (mL)**	**Part A**	**Part B, Cohort 1**	**Part B, Cohort 2**	**Part B, Cohort 3**	**Part B, Cohort 4**
Blood sampling period		**Day-30 – Day4**	**Day-30 – Day15**	**Day-30 – Day16**	**Day-30 – Day14**	**Day-30 – Day14**
Coagulation parameters	[redacted]					
Hematology						
Clinical chemistry test						
Virology						
Serum pregnancy test						
Platelet function test						
CYP2C19 genotyping						
PK samples of LT3001						
PK samples of Aspirin,						

Clopidogrel Apixaban, or Dabigatran						
[redacted]						

Note: An indwelling intravenous cannula may be used for blood sample collection. If a mandarin (obturator) is used, blood loss due to discard is not expected. If blood samples are collected via an indwelling cannula, an appropriate amount (i.e., 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or study. The severity or intensity of each AE is to be assessed by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0

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9.1.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

9.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose.

If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2. Treatment of Overdose

The dose level of LT3001 drug product will be calculated by the Investigator or a qualified designee based on the study subject's body weight. Since drug accumulation is not anticipated due to the short half-life of LT3001 and subjects will only receive LT3001 drug product administered by an Investigator or a qualified designee and under close monitoring, it is anticipated that the risk of overdose or medication error will be low.

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

Overdoses and medication errors will be documented as protocol deviations and communicated to the project manager.

No specific therapy for overdose of LT3001 drug product exists. In the event of overdose or medication error, appropriate therapy for the patient's symptoms and clinical status should be provided.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Vital Signs

- Body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate will be assessed after the subject has rested in position 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.
- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.3.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, and QTcF intervals.
- ECG will be measured in a supine position after 5 minutes rest.

9.3.4. Pulse Oximetry

During Part A, 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).

9.3.5. Coagulation and Platelet Function Test

During Part A, platelet function test will measure on Day -1, following the first (Dose 1) and last (Dose 9) dose of LT3001 drug product infusion and end of study visit. Coagulation (PT, INR, aPTT, and TT) will be measured during screening, Day -1, and following the Dose 1, 4, and 9 of LT3001 drug product infusion and follow-up visit.

During Part B, coagulation test will be measured in the screening visit. Platelet function test and coagulation tests will be measured on Day -1, following the last dose of aspirin, clopidogrel, apixaban, and dabigatran 15 minutes and 6 hours 15 minutes, and following aspirin, clopidogrel, apixaban and dabigatran coadministration with the first and last LT3001 drug product infusion and follow-up visit.

9.3.6. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4. Pharmacokinetics

Whole blood and urine samples will be collected for measurement of plasma and urine concentrations of LT3001 as specified in the SoA (Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

The following PK parameters will be estimated as practicable using actual sample collection times:

C_{max}	maximum plasma concentration during a dosing interval
C_{min}	trough plasma concentration
C_{av}	mean steady-state drug concentration
t_{max}	time to reach the maximum 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
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinite time, calculated as the sum of AUC_{last} and C_{last}/λ_z, in which C_{last} is the last observed quantifiable concentrations
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours, calculated by the linear trapezoidal linear interpolation method
AUC_{0-tau}	AUC over the dosing interval τ at steady-state
$MRT_{0-\infty}$	Mean residence time, calculated as $\frac{AUMC_{0-\tau}+\tau(AUC_{0-\infty}-AUC_{0-\tau})}{AUC_{0-\tau}}-\frac{TI}{2}$ where $AUMC_{0-\tau}$ is the area under the moment curve over dosing interval τ, 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
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
CLr	Renal clearance, calculated as Ae_{0-24} / $AUC_{0-\infty}$
Racc	Accumulation ratio calculated as $AUC_{0-t,\ 1st\ dose}/AUC_{0-t,\ last\ dose}$ for the multi-day LT3001 regimens.

9.5. Pharmacogenetics

For Part B Cohort 2 only, a blood sample for identification of CYP2C19 poor metabolizers (CYP2C19*2/*2, *2/*3, or *3/*3 genotype) will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is mandatory for Part B Cohort 2.

9.6. Medical Resource Utilization and Health Economics

Not applicable

10. Statistical Considerations

10.1. Sample Size Determination

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.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

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 else than aspirin/clopidogrel/apixaban/dabigatran, protocol deviations of diet restriction).

10.3. Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the endpoints. Baseline value is defined as the last non-missing measurement prior to the initiation of any study treatment unless specified elsewhere.

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Adverse events will be coded by System Organ Class and Preferred Term using the latest version of MedDRA. Incidences of TEAEs (ie, events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose group, maximum severity, and relationship to study medication.

Safety data will be summarized through appropriate data tabulations and standard descriptive statistics by treatment. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Shift tables capturing the number and percentage of subjects shifting from these baseline to post-baseline categories will be presented.

The association of AEs, laboratory results, coagulation parameters, platelet function test, vital sign measurements, oximetry, and ECG results with the treatment of study drug or PK parameters may also be explored. If appropriate, statistical modeling will be performed to further characterize the associations mentioned above. All out-of-range and clinically significant laboratory results will be identified in subject data listings. The number and percentage of subjects in each dose group with normal and abnormal physical examination results will be presented for evaluations at baseline and final visit.

For each body system, changes in the subjects' findings from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be tabulated for each dose group.

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 compared with platelet function test observed under coadministration with LT3001 drug product. Platelet function test will be summarized with standard descriptive statistics by treatment. Shift tables capturing the number and percentage of subjects shifting from baseline to post-baseline categories will be presented.

10.3.2. Pharmacokinetic Analyses

All PK analyses will be performed on the Pharmacokinetic Analysis Set. The PK parameters will be calculated, as appropriate, using a non-compartmental approach.

Plasma concentrations will be summarized by cohort over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus actual time points will be presented in listings. Pharmacokinetic parameters will be summarized by dose using descriptive statistics. Individual PK parameters will be presented in a data listing.

The effect of aspirin, clopidogrel, apixaban or dabigatran on the PK of LT3001, as well as the effect of LT3001 on the PK of aspirin, clopidogrel, apixaban or dabigatran, will be assessed by comparing PK parameters of LT3001 and these concomitant medications. A linear mixed-effects model with fixed factors for Cohort and Day (day of with/without concomitant drug use), and subject as random effect on log PK-parameter will be used to calculate 90% confidence intervals for the geometric mean ratio of the $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tau}$ and C_{max}. Differences between treatments when LT3001 drug product was administered alone or with aspirin, clopidogrel, apixaban or dabigatran will be calculated for LT3001, aspirin, clopidogrel, apixaban, and dabigatran using ratios of geometric least squares mean and 90% confidence intervals (CI). The criteria of 90% CI within 50-200% of weak-effect boundaries will be firstly used 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.

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. The comparisons will be conducted for occasions when LT3001 is alone or is coadministrated with aspirin, clopidogrel, apixaban, or dabigatran. PK parameters for comparison include AUC_{0-t} and C_{max}..

11. References

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12. Appendices

Appendix 1: Abbreviations and Terms

Abbreviation	Definition
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)
AIS	acute ischemic stroke
aPTT	activated partial thromboplastin time
AUC	area under the 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 time point 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 limit of quantification
CFR	Code of Federal Regulations
C_{av}	Mean steady-state drug concentration
CL	total body clearance
CLr	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	Trough plasma concentration
CRF	case report form
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
Fe_{0-24}	fraction excreted in urine from 0 to 24 hours after dosing
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HV	healthy volunteer
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committees

IRB	institutional review board
IV	intravenous
λz	apparent first-order terminal elimination rate constant
MRT	mean residence time
n	number of observations
PAF	platelet activation factor
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PT	prothrombin time
q12h	every 12 hours
q3h	3 hours apart
rtPA	recombinant tissue-type plasminogen activator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SoA	schedule of activities
SRM	Safety Review Meeting
TEAE	treatment-emergent adverse event
TID	three times a day
TT	thrombin time
t_{max}	time to reach the observed maximum (peak) concentration
$t_{1/2}$	elimination half-life
US	United States
V_{ss}	volume of distribution at steady state
Vz	Apparent volume of distribution during the terminal phase

Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 Protocol-Required Safety Laboratory Assessments8 will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 8 Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet Count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices</u>:
Mean Corpuscular Volume
Mean Corpuscular Hemoglobin</td><td><u>White blood cell count with differential</u>:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">alkaline phosphatase (ALP)
alanine aminotransferase (ALT)
aspartate aminotransferase (AST)
gamma-glutamyl transferase (GGT),</td></tr>
<tr><td>Clinical Chemistry</td><td>blood urea nitrogen (BUN)
creatinine
fasting blood glucose
total bilirubin
total proteins
albumin/globulin ratio,</td><td>sodium (Na)
potassium (K)
chloride (Cl)
calcium (Ca),
bicarbonate
uric acid</td><td>creatine kinase (CK),
cholesterol
triglycerides
free iron
ferritin</td></tr>
<tr><td>Platelet Function</td><td colspan="3">• Platelet function test</td></tr>
<tr><td>Coagulation</td><td colspan="3">• Prothrombin time
• Activated partial thromboplastin time
• International Normalized Ratio
• Thrombin time</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="3">• Specific gravity</td></tr>
</table>

	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum human chorionic gonadotropin (hCG) pregnancy test • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests) • Covid-19 • CYP2C19 genotyping test

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

Consent for Covid-19 testing

- A consent form for Covid-19 testing will be sent electronically to potential participants before scheduling screening. Testing is mandatory for all participants.
- The participants will date and sign the form and bring it with them on the first day of screening.

Consent to participate in the study

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local

regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

A clinical study report will be prepared with reference to ICH Guidance E3 to include:

- details of where the study was carried out,
- dates of the start and completion of each period of the study,

- details of the investigational product (IP) and a statement of production will be provided by Lumosa
- a statement confirming that the applicable IRB/IEC gave written approval for the study in accordance with local regulations,
- a demographic listing for all participants,
- a list of all AEs according to IP,
- details of any occurrences which may be of significance to the study outcome,
- details of all operations, calculations and transformations performed on the reported data,
- the SAP and report will be produced by Lumosa or their agents and will be incorporated into the final report,
- all data from any withdrawn participant not included in the statistical analysis,
- a scientific interpretation of the results,
- a description of the study methods used.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Study Manual.

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent

one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Lumosa in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Lumosa. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Lumosa.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of severity

The severity or intensity of each AE is to be assessed by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Grade refers to the severity of the AE. The CTCAE displays Grade 1 through 5 with unique clinical descriptions of severity for each AE based on this general guidance:

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.

- Grade 5 Death related to AE.

  Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

  Self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Lumosa. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** Lumosa**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Classification of Adverse Events by Relationship to Study Treatment

- **UNRELATED:** This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
- **UNLIKELY:** This category applies to those AEs that are judged to be unrelated to the test drug/study procedure but for which no extraneous cause may be found. An AE may be considered unlikely to be related to investigational product /procedure if or when it meets 2 of the following criteria: (1) it does not follow a reasonable

temporal sequence from administration of the test drug /study procedure; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug/study procedure; or (4) it does not reappear or worsen when the drug/study procedure is readministered.

- **POSSIBLY:** This category applies to those AEs for which a connection with the test drug /study procedure administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug /study procedure.
- **PROBABLY:** This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug /study procedure. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug/study procedure.
- **DEFINITELY:** This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug/study procedure. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug /study procedure.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Lumosa to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Lumosa with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to Lumosa within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Lumosa via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Lumosa will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the Study Manual.

SAE Reporting to Lumosa via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Manual.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 6.1]:

Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in **Table** 9 Highly Effective Contraceptive Methods9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Refrain from donating sperm for the duration of the study and for 30 days after the last dose of LT3001 drug product.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9 Highly Effective Contraceptive Methods9.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion Bilateral tubal ligation Hormonal or non-hormonal Intrauterine device (IUD)
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at 30 days after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LT3001 drug product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the sponsor as described in Section 9.1. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.