Protocol Full Title:	A Phase 1 Study to Evaluate Relative Bioavailability and Food Effect of an ALG-097558 Tablet Formulation and the Drug-Drug Interaction Potential of ALG-097558 and its metabolite ALG-097730 in Healthy Volunteers
Protocol Number:	24-0026
Version Number:	3.0
Amendment Number:	Not applicable
Version/Amendment Scope:	Global
Compound Name(s):	ALG-097558
Trial Phase:	Phase 1
Short Title:	Phase 1 Study on Bioavailability, Food Effect, and Drug-Drug Interaction of ALG-097558 Tablets in Healthy Volunteers
Sponsor Name and Address:	Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, USA
Regulatory Agency Identifier Number(s):	IND:176089 NCT069945276
Version Date:	12/Jun/2025

Contact information of key members for this trial including the Medical Monitor can be found in the study manual of operating procedures (MOP).

Amendment Details

History of Amendments

Document	Version Date (dd/mmm/yyyy)
Original Protocol	27/Feb/2025
Amendment 1	22/Apr/2025

Current Amendment

The following table provides an overview of the current amendment.

Amendment Number:	Amendment #2
Reasons for Amendment:	Primary: Inconsistency and/or error in the protocol
Summary of the Amendment:	Update to be consistent with timing of study events, deviation reporting, and removal of conflicting information.

Summary of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change
1.3 – Schedule of Activities	Updates to footnotes throughout	Consistent information between study parts and with the text regarding pk blood collection for analysis and protocol deviation windows
8.3.5 – Clinical Laboratory Assessments	Removing the following from the protocol, "If abnormal, non-clinically significant clinical laboratory values worsen from the baseline value, this will be reported as an AE . . ."	Removal of conflicting information to avoid confusion

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federal Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) for federally funded research. The IRB/IEC must be registered with OHRP as applicable to the research.

The trial will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 (Electronic Records and Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and DMID
- The National Institute of Allergy and Infectious Diseases (NIAID) Terms of Award
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, U.S. federal regulations, and ICH E6(R2) Good Clinical Practice (GCP) guidelines.

Site Investigator Signature:			
Signed:		Date:	
	<Print Name, Credentials> <Print Title>		

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1. PROTOCOL SUMMARY

1.1 Protocol Synopsis

Rationale

COVID-19 is an infectious disease caused by the virus SARS-CoV-2. As of February 2024, more than 774 million confirmed cases of COVID-19 were reported worldwide, including 7 million deaths (WHO COVID-19 Dashboard) in which safe, effective, and convenient treatments for acute infection are needed. Paxlovid is the current standard of care oral antiviral agent for the treatment of mild-to-moderate COVID-19 and is a combination of the orally bioavailable protease inhibitor nirmatrelvir with ritonavir (RTV), a strong cytochrome P450 (CYP) 3A4 inhibitor. Despite its demonstrated efficacy, a major limitation of Paxlovid is drug-drug interactions (DDI), caused primarily by RTV, which limits its use in patients with other co- morbidities who are receiving concomitant medications that cannot be stopped/modified. Thus, safe and effective oral therapeutics that can be used in an outpatient setting without risks of DDIs or significant contraindications are still required for management of COVID-19.

ALG-097558 is a selective, reversible, and potent inhibitor of the SARS-CoV-2 3CLpro with pan-coronavirus activity. Toxicologic effects noted in nonclinical studies at very high systemic exposures were reversible and monitorable. Human efficacious plasma exposures can be achieved without any need for RTV boosting at doses of 200 to 600 mg BID and still maintain a wide safety margin relative to the no observed adverse effect level (NOAEL) from the repeat- dose toxicology studies. ALG-097730 was the major oxidative metabolite of ALG-097558 that was detected in several nonclinical species and demonstrated 4- to 30-fold reduced antiviral activity compared with ALG-097558. At clinically relevant projected plasma exposures, the key DDI risk is expected to be due to CYP induction by ALG-097558 (CYP2B6 ≥1 μM and CYP3A4 ≥0.33 μM) and ALG-097730 (CYP2B6 and CYP3A4 ≥10 μM each); CYP3A inhibition (by ALG-097558 only); interaction of ALG-097558 and ALG-097730 as Permeability-glycoprotein (P-gp) substrates; and ALG-097558 as a CYP3A substrate. The risk- benefit profile, as determined by available nonclinical data and safety and PK data in healthy volunteers enrolled in Study ALG-097558-701, remains favorable and supportive of the continued evaluation of ALG-097558, including in subjects with COVID-19.

Primary and Secondary Objectives and Endpoints

Part A – DDI-Itraconazole

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	

Evaluate the effect of a CYP3A4 inhibitor/P-gp inhibitor, itraconazole, on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	PK parameters of ALG-097558 and metabolite ALG-097730 in plasma, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following single dose administration

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	alone or with co-administration of multiple dose itraconazole
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in healthy volunteer (HV) participants when administered as monotherapy or in combination with itraconazole	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)

Part B – DDI-Dabigatran

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
Evaluate the effect of multiple doses of ALG-097558 on the pharmacokinetics of a P-gp substrate, dabigatran	PK parameters of dabigatran (total) in plasma, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following single dose administration alone or with co-administration of multiple dose ALG-097558
Secondary	

Evaluate the safety and tolerability and PK of multiple doses of ALG-097558 in HV participants when administered alone or in combination with dabigatran	• Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis) PK parameters of ALG-097558 and ALG-097730, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following administration of multiple dose ALG-097558

Part C – Relative BA and Food Effect

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
Evaluate the relative bioavailability of 2 different tablet formulations of ALG-097558 and effect of food on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	PK parameters of ALG-097558 and the metabolite ALG-097730 in plasma, including but not limited to $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, T_{lag}, C_{max}, and $t_{1/2}$, following single dose administration of Tablet Formulations 1 and 2 of ALG-097558 and following administration of a high-fat diet (Tablet Formulation 2)
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in HV participants	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment), vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)

For a full list of Objectives/Endpoints, see Section 3.

Trial Design

Interventional Study Product(s):	ALG-097558

Intervention Model:	Single Group for Part A and Part B, Crossover with 3 arms in Part C
Population Type:	Healthy volunteer
Population Diagnosis or Condition:	N/A – Healthy
Population Age:	18 – 65 years old
Control:	Single-blind placebo in Part A only
Active Comparator:	N/A
Number of Arms:	1 arm in Part A, 1 arm in Part B, and 3 arms in Part C
Number of Participants:	Number enrolled in Part A: 12 participants Number enrolled in Part B: up to 24 participants Number enrolled in Part C: 15 participants
Trial Intervention Assignment Method:	Open-label with Single Blind in Part A and Randomization to 3 different Crossover arms in Part C
Site Distribution:	Single-site
Blinding:	The roles indicated below will be unaware of the treatment group assignment during the trial: • Participants in Part A Not applicable (No blinding) for all other parts.
Participant Duration:	Including the screening period, the total duration for each participant is up to 49 days depending on which part of the study the participant is enrolled.

Study Arms

Please refer to the Study Schemas for study arms by study part (Section 1.2).

Trial Duration

The estimated duration of the trial is 6 months.

Committees:

No independent committees will be reviewing the data while the trial is ongoing. This protocol will use a Protocol Safety Review Team (PSRT), which is an advisory group internal to this trial that may be used for the protocol decision steps based on safety data and other factors that require the team's input and deliberation. The PSRT is composed of the Principal Investigator (PI), DMID Medical Monitor (MM), and DMID Medical Officer (MO). Representatives from the drug developer may be included as non-voting members of the PSRT. PSRT will be reviewing the data while the trial is ongoing.

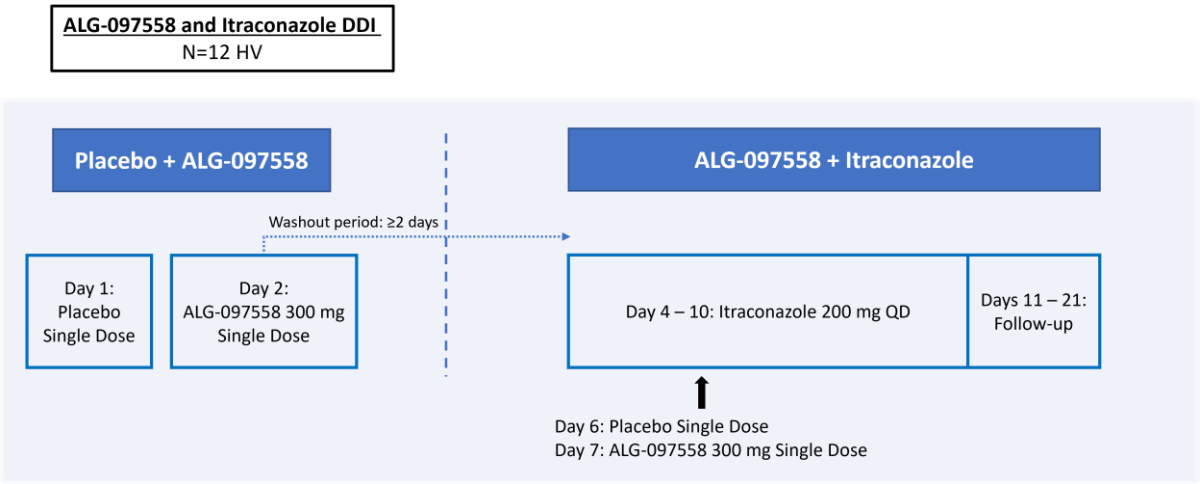
Independent Committees: N/A

See Section 10.2.

1.2 Trial Schema

1.2.1 Part A: DDI-Itraconazole

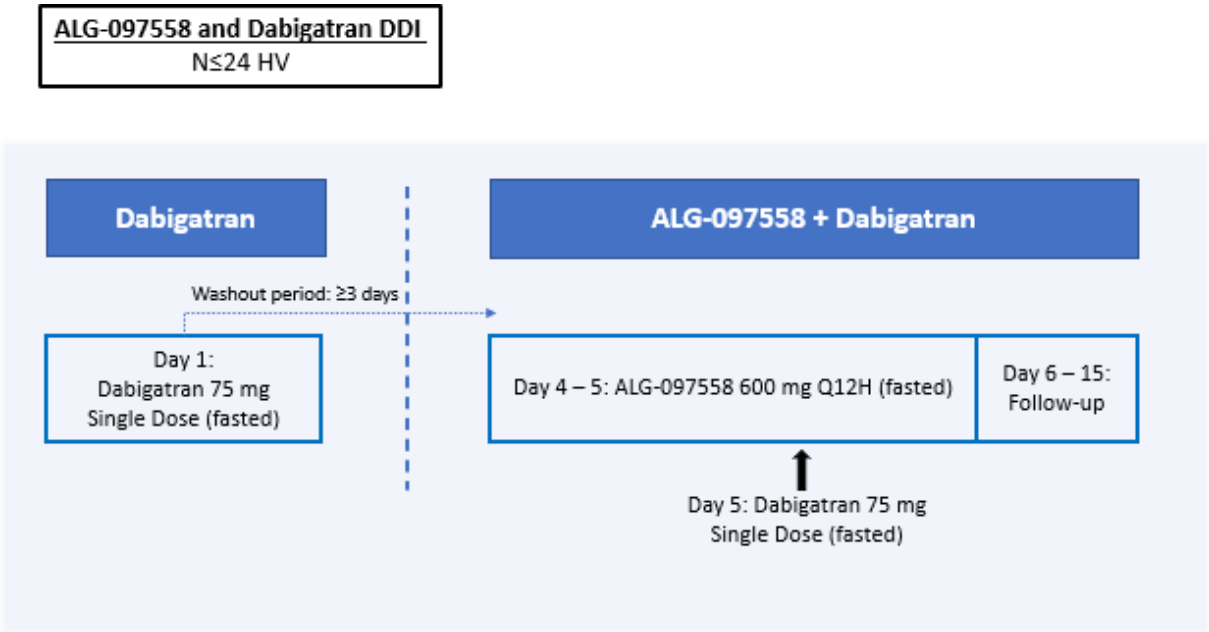
Figure 1. Schematic for Part A: DDI-Itraconazole of 24-0026



ALG-097558 Tablet Formulation 1 (spray-dried dispersion tablet) to be used in this part to be given in a fasted state

1.2.2 Part B: DDI-Dabigatran

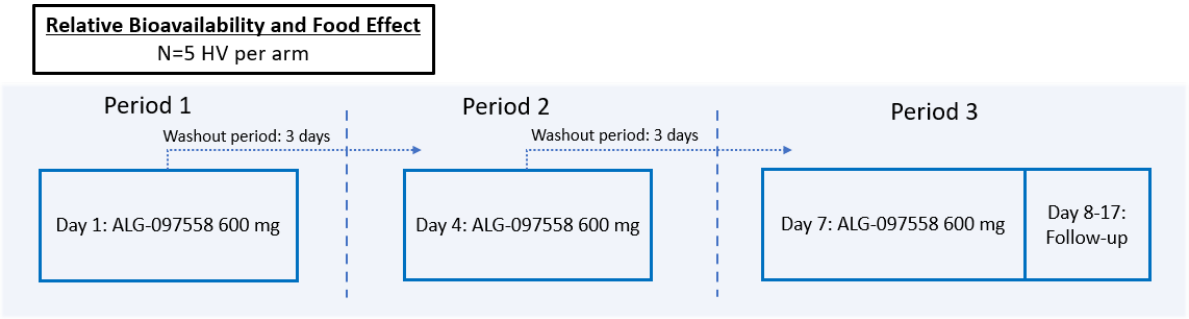
Figure 2. Schematic for Part B: DDI-Dabigatran of 24-0026



ALG-097558 Tablet Formulation 1 (spray-dried dispersion tablet) to be used in this part.

1.1.1 Part C: Relative Bioavailability and Food Effect

Figure 3. Schematic for Part C: Relative Bioavailability and Food Effect of 24-0026



There will be three arms with different formulation and dose conditions at the three periods in this part. One treatment will be ALG-097558 Tablet Formulation 1 (spray-dried dispersion tablet) in fasted state, another will be Tablet Formulation 2 (conventional tablet) in the fasted state, and the last treatment will be Tablet Formulation 2 in the fed state. Each arm will receive these treatments in a different order.

Participants will be randomized equally (1:1:1) into one of three treatment sequences:

Arm	**Period 1**	**Period 2**	**Period 3**
Sequence 1	Formulation 1 fasted	Formulation 2 fasted	Formulation 2 fed
Sequence 2	Formulation 2 fasted	Formulation 2 fed	Formulation 1 fasted
Sequence 3	Formulation 2 fed	Formulation 1 fasted	Formulation 2 fasted

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Part A: DDI-Itraconazole

Table 1. Schedule of Activities for Part A: DDI-Impact of Itraconazole (CYP3A4/P-gp Inhibitor) on Pharmacokinetics of ALG-097558 and ALG-097730

Assessment [a] \ Day / Hour	Screening	Check-In	Days 1 and 2 (Hour Relative to Dosing)											3
	-28 to -2	-1	Predose	0	0.25	0.5	1	2	3	4	6	8	12	
Obtain informed consent before study procedures	X													
Demographics	X													
Medical/surgical history	X	X (interim)												
HIV-1, HIV-2, Hep A, B, C, & E tests [b]	X													
Drug, cotinine, and alcohol screening [b]	X	X												
Pregnancy testing [c]	X	X												
FSH testing [c]	X													
Confirm eligibility [d]	X	X	X											
Outpatient visits	X													
Confined to study site		X	X											X
Enrollment [e]		X												
Placebo (for ALG-097558) administration [f]				**X (Day 1)**										
ALG-097558 administration [f]				**X (Day 2)**										
Physical examination [g]	X	X					X							X
12-lead ECG [a,h]	X	X	X		X	X	X	X	X	X	X	X	X	X
Holter monitoring [i]			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [a, j]	X	X	X			X	X	X		X		X		X
Safety labs [a,k]	X	X												X
ALG-097558 plasma PK sampling [a,l]			X		X	X	X	X	X	X	X	X	X	X
Adverse events	X													
Concomitant medication	X													

																	Check-out[m] /EOT	**Follow-up /EOS**
	4	**5**	**Days 6 and 7 (Hour Relative to Dosing)**											**8**	**9**	**10**	**11**	**21±1**
Day / Assessment			**Pre dose**	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**					
Outpatient visits																		X
Confined to site								X									X	
Itraconazole administration [f]	**X**	**X**		**X**										**X**	**X**	**X**		
Placebo (for ALG-097558) administration [f]				**X (Day6)**														
ALG-097558 administration [f]				**X (Day7)**														
Physical exam [g]	X	X					X							X	X	X	X	X
12-lead ECG [a,h]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Holter monitoring [i]			X	X	X	X	X	X	X	X	X	X	X	X				
Vital signs [a,j]	X	X	X			X	X	X		X		X		X	X	X	X	X
Safety labs [a,k,n]		X													X			X
ALG-097558 and ALG-097730 plasma PK sampling [a,l]	X		X		X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X																	
Concomitant medication	X																	

[a] If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling. Blood collections for PK assessments should be kept as close to the specified time point as possible. Predose procedures (unless otherwise specified) will be collected within 60 minutes of dosing time. A protocol deviation will not be recorded unless procedures are done greater than 60 minutes prior to dosing. All efforts will be made to obtain PK samples at the exact nominal time relative to dosing. Protocol deviations will be recorded if the PK sample is collected more than +/- 10 minutes from nominal time. Exact time of collection will be noted on source document and data collection record (e.g., CRF). All efforts will be made to collect Vital signs and ECGs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs and/or ECGs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[b] Refer to Section 8.1 for additional information on serology and drug, cotinine, and alcohol screening. Note that Hep E test will only be conducted on participants who have been to an endemic region for Hep E in the last 90 days.

[c] Serum pregnancy test for women of childbearing potential at Screening and urine testing at other visits that require pregnancy testing. Positive urine test should be confirmed by serum pregnancy test. Women of postmenopausal status should have FSH levels tested for confirmation at Screening.

[d] If a subject's clinical status changes or does not meet all inclusion/exclusion criteria before the first dose of study drug, including applicable Day –1/Day 1 assessments, the subject will not be enrolled into the study.

[e] Enrollment can occur any time predose.

[f] Subjects will receive a single PO dose of matching placebo for ALG-097558 (morning of Day 1), and a single PO dose of ALG-097558 300 mg (morning of Day 2). After a washout period, multiple PO doses of Itraconazole 200 mg QD for 7 days (mornings of Day 4-10), a single PO dose of matching placebo for ALG-097558 (morning of Day 6), and a single PO dose of ALG-097558 300 mg (morning of Day 7). A dosing window of ±1 hour within the nominal time will be allowed for administration of the study medication(s). Administration of itraconazole and ALG-097558 will be in the fasted state at the same time on dosing days.

[g] A complete physical examination (including height at screening only and body weight measurement) will be performed at screening and Day 21. A symptom-directed physical examination will be performed at any time as indicated at all other visits.

[h] Triplicate 12-lead ECGs will be collected during screening and predose on Day 1, 2, 6, and 7. Subjects must have been resting in the supine fashion for at least 5 minutes. When a 12-lead Holter device is also in use, triplicate ECGs will be extracted from the Holter for safety monitoring. A regular ECG will be used for all other timepoints.

[i] Holter monitoring will be collected ~2-hour predose (Day 1) through 24 hours post-Day 2 dose, on Day 3. The same will occur again ~2-hour predose on Day 6 through 24 hours post-Day 7 dose on Day 8. Each continuous ECG recording will be performed for approximately 49.25 hours, starting 1.25-hour predose on Day 1 and on Day 6. Continuous ECGs will be extracted at a central ECG laboratory at the following time points, paired with PK determinations: at 3 time points within 1.25 hours prior to dosing (e.g., -1.25, -1.0, and -0.75 hours) and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose (Day 2 and Day 8). Subjects will be resting in a supine position for at least 5 minutes before and 5 minutes after each time point.

[j] Vital signs (oral temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate): will be measured in the supine position after resting for at least 5 minutes. Vital signs will be collected daily during confinement with multiple collections on Days 1, 2, 6 and 7 (predose, and at 0.5, 1, 2, 4, 8 hours postdose) or at any time for other visits depicted in the table or pre-morning dose, if not defined in the table. On dosing days, vital sign measurements will be **collected within 2 hours** prior to treatment administration. All efforts will be made to collect Vital signs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[k] To include a complete blood count with differential, comprehensive metabolic panel, coagulation and urinalysis see Table 4 in Section 8.3.5 for details. If any urinalysis is positive, urine will need to be sent for microscopy sensitivity. Samples for serum chemistry will be obtained after a fast of at least 10 hours, however, in case of rechecks, participants may not have fasted for 10 hours prior to when the serum chemistry sample is taken. It will be recommended for Screening labs that the participant to be in the fasted state but if the participant is not in the fasted state this will not be a protocol deviation.

[l] PK plasma samples for ALG-097558 and ALG-097730 are collected on both Day 1 and Day 2 (placebo and active dosing days) within 60 minutes predose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8,12, 24 (Day 3), 48 (Day 4) hours post dose; and on Days 6 and 7 60 minutes predose, and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 8), 48 (Day 9), and 72 (Day 10) hours postdose. On Day 8 through Day 10, the collection will be within 1 hour of the time of second dose of ALG-097558.

[m] If a subject discontinues administration of study medication, the subject is strongly encouraged to continue to attend the postdosing/follow-up visits; in this case, the Study Day of this visit would be based on maintaining the same time since last dose rather than being performed on the Study Day indicated in the schedule of assessments. In case of withdrawal from the study, subjects should return to the study site for a Withdrawal/Early Termination visit (same assessments as Day 11) as soon as possible, preferably within ≤72 hours.

[n] Safety labs and urinalysis may be collected at any time predose on Day 9.

Abbreviations: ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; PK=pharmacokinetics; PO=oral; QD=once daily.

1.3.2 Schedule of Activities for Part B: DDI-Dabigatran

Table 2. Schedule of Activities for Part B: DDI- Impact of ALG-097558 on Pharmacokinetics of Dabigatran (P-gp Substrate)

	Screening											
		Check-In										
Day	**-28 to -2**	**-1**	**Day 1 (Hour Relative to Dosing)**								**2**	**3**
Assessment [a]			**Predose**	**0**	**1**	**2**	**4**	**6**	**8**	**12**		
Obtain informed consent before study procedures	X											
Demographics	X											
Medical/surgical history	X	X (interim)										
HIV-1, HIV-2, Hep A, B, C, & E tests [b]	X											
Drug, cotinine, and alcohol screening [b]	X	X										
Pregnancy test [c]	X	X										
FSH testing [c]	X											
Confirm eligibility [d]		X										
Outpatient visits	X											
Confined to study site		X	X									
Enrollment [e]		X										
Dabigatran administration [f]				**X**								
Physical examination [g]	X	X				X					X	X
12-lead ECG [a,h]	X	X	X		X	X	X					X
Vital signs [a,i]	X	X	X		X	X	X				X	X
Safety labs [a,j,o]	X	X										X
Dabigatran Plasma PK sampling [a]			X		X	X	X	X	X	X	X (24 h and 36 h post)	X (48 h post)
Adverse events	X											
Concomitant medication	X											

	(Washout of ≥3 days [≥72 hours] between dosing on Study Days 1 and 4)												
Day	**4 [k]**	**Day 5/ (Hour Relative to Dosing)**								**6**	**7**	**Check-out 8/EOT**	**Follow-up[l,m] 15±1/EOS**
Assessment		**Predose**	**0**	**1**	**2**	**4**	**6**	**8**	**12**				
Confined to study site						X				X	X	X	
Outpatient visits													X
ALG-097558 administration [f]	**X**		**X**										
Dabigatran administration			**X**										
Physical examination [g]	X				X					X	X	X	X
12-lead ECG [a,h]		X		X	X	X						X	X
Vital signs [a,i]	X	X		X	X	X				X	X	X	X
Safety labs [a,k,o]												X	X
Pregnancy test [c]													X
ALG-097558 and ALG-097730 plasma PK sampling [a]		X		X	X	X	X	X	X	X (24 h post)			
Dabigatran plasma PK sampling [a]	X (72 h post) [n]	X		X	X	X	X	X	X	X (24 h and 36 h post	X (48 h post)	X (72 h post)	
Adverse events	X												
Concomitant medication	X												

[a] If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling. Blood collections for PK assessments should be kept as close to the specified time point as possible. Predose procedures (unless otherwise specified) will be collected within 60 minutes of dosing time. A protocol deviation will not be recorded unless procedures are done greater than 60 minutes prior to dosing. All efforts will be made to collect Vital signs and ECGs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs and/or ECGs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).
. PK samples for ALG-097558 and ALG-097730 are collected on Day 5 within 60 minutes predose 5 , and postdose at 1, 2, 4, 6, 8, and 12 hours postdose, and on Day 6 the collection will be 24 hours post dose on Day 5. PK samples for dabigatran are collected on Day 1 and Day 5 predose at -0.75 hours, and postdose at 1, 2, 4, 6, 8, and 12 hours postdose, On Day 2, the collections will be at 24 and 36 hours post dose on Day 1. On Day 3, the collection will be 48 hours post dose on Day 1. On Day 4, the collection will be 72 hours post dose on Day 1. On Day 6, collections at 24 and 36 hours post dose on Day 5. On Day 7, the collection will

be 48 hours post dose on Day 5. On Day 8, the collection will be 72 hours post dose on Day 5. All efforts will be made to obtain PK samples at the exact nominal time relative to dosing. Protocol deviations will be recorded if the PK sample is collected more than +/- 10 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[b] Refer to Section 8.1 for additional information on serology and drug, cotinine, and alcohol screening. Note that Hep E test will only be conducted on participants who have been to an endemic region for Hep E in the last 90 days.

c Serum pregnancy test for women at Screening and urine testing at other visits that require pregnancy testing. Positive urine test should be confirmed by serum pregnancy test. Women of postmenopausal status should have FSH levels tested for confirmation at Screening.

[d] If a subject's clinical status changes or does not meet all inclusion/exclusion criteria before the first dose of study drug, including applicable Day –1/Day 1 assessments, the subject will not be randomized into the study.

[e] Enrollment can occur any time predose.

[f] Subjects will receive a single PO dose of dabigatran 75 mg in the morning of Day 1, and after a washout period, multiple PO doses of ALG-097558 600 mg every 12 hours (i.e., once in the morning and once in the evening) on Day 4 and one morning dose on Day 5 for a total of 3 doses, and a single PO dose of dabigatran 75 mg (morning of Day 5). A dosing window of ±1-hour within the nominal time will be allowed for administration of the study medication(s).

[g] A complete physical examination (including height at screening only and body weight measurement) will be performed at screening and Day 15. A symptom-directed physical examination will be performed at any time as indicated at all other visits.

[h] Single 12-lead ECGs will be collected during screening and at specified times depicted in table. Subjects must have been resting in the supine fashion for at least 5 minutes.

[i] Vital signs (oral temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate): will be measured in the supine position after resting for at least 5 minutes. For time periods associated with PK collection, vital signs should be collected before PK blood draw or 15 minutes afterwards. On dosing days, vital sign measurements will be **collected within 2 hours** prior to treatment administration. All efforts will be made to collect Vital signs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[j] If any urinalysis is positive, urine will need to be sent for microscopy sensitivity.

[k] First day of dosing with ALG-097558 will always be denoted as Study Day 4, even if washout is required to exceed 3 days (72 hours).

[l] A window of ±1 days is allowed for the scheduling of this visit.

[m] If a subject discontinues administration of study medication, the subject is strongly encouraged to continue to attend the postdosing/follow-up visits; in this case, the Study Day of this visit would be based on maintaining the same time since last dose rather than being performed on the Study Day indicated in the schedule of assessments. In case of withdrawal from the study, subjects should return to the study site for a Withdrawal/Early Termination visit (same assessments as Day 8) as soon as possible, preferably within ≤72 hours.

[n] If greater than 3 days (72 hours) of washout are required, dabigatran PK samples should be drawn 72 hours after the dabigatran dose. Must be performed prior to dosing of ALG-097558 on Day 4.

[o] To include a complete blood count with differential, comprehensive metabolic panel, coagulation and urinalysis see Table 4 in Section 8.3.5. Samples for serum chemistry will be obtained after a fast of at least 10 hours, however, in case of rechecks, participants may not have fasted for 10 hours prior to when the serum chemistry sample is taken. It will be recommended for Screening labs that the participant to be in the fasted state but if the participant is not in the fasted state this will not be a protocol deviation.

Abbreviations: : ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; PK=pharmacokinetics; PO=oral; QD=once daily.

1.3.3 Schedule of Activities for Part C: Relative Bioavailability and Food Effect

Table 3. Schedule of Activities for Part C: Relative Bioavailability of ALG-097558 Tablet Formulations and Food Effect

Day	Screening	Check-In	Day 1, Period 1 (Hour Relative to Dosing)											2	3
Assessment [a]	-28 to -2	-1	Predose	0	0.25	0.5	1	2	3	4	6	8	12		
Obtain informed consent before study procedures	X														
Demographics	X														
Medical/surgical history	X	X (interim)													
HIV-1, HIV-2, Hep A, B, C, & E tests [b]	X														
Drug, cotinine, and alcohol screening [c]	X	X													
Pregnancy testing [d]	X	X													
FSH testing [d]	X														
Confirm eligibility [e]		X													
Outpatient visits	X														
Confined to study site		X	X												
Enrollment/randomization [f]		X													
ALG-097558 administration [g]				**X**											
Physical examination [h]	X	X						X						X	X
12-lead ECG [a, i]	X	X	X			X		X							
Vital signs [a, j]	X	X	X					X						X	X
Safety Labs [a.k]	X	X													X
ALG-097558 and ALG-097730 metabolite Plasma PK sampling [a, l]			X		X	X	X	X	X	X	X	X	X	X (24 h post)	X (48 h post)
Adverse events	X														
Concomitant medication	X														

Day	**Day 4, Period 2 (Hour Relative to Dosing)**											**5**	**6**
Assessment [a]	**Predose**	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**		
Confined to study site	X												
ALG-097558 administration [g]		**X**											
Physical examination [h]						X						X	X
12-lead ECG [a,i]	X			X		X							
Vital signs [a,j]	X					X						X	X
Safety labs [a,k]													X
Pregnancy test[d]	X												
ALG-097558 plasma PK sampling [a,l]	X		X	X	X	X	X	X	X	X	X	X (24 h post)	X (48 h post)
Adverse events	X												
Concomitant medication	X												

Day	Day 7, Period 3 (Hour Relative to Dosing)											8	Check-Out/EOT[m] 9	Follow-Up/EOS 17±1
Assessment	**Predose**	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**			
Outpatient Visit														X
Confined to study site							X							
ALG-097558 administration[g]		**X (fed)**												
Physical examination [h]						X						X	X	X
12-lead ECG [a,i]	X			X		X							X	X
Vital signs [a,j]	X					X						X	X	X
Safety labs [a,k]													X	X
Pregnancy test [d]	X													X
ALG-097558 plasma PK sampling [a,l]	X		X	X	X	X	X	X	X	X	X	X (24 h post)	X (48 h post)	
Adverse events	X													
Concomitant medication	X													

[a] If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling. Predose procedures (unless otherwise specified) will be collected within 60 minutes of dosing time. A protocol deviation will not be recorded unless procedures are done greater than 60 minutes prior to dosing. All efforts will be made to obtain PK samples at the exact nominal time relative to dosing. Protocol deviations will be recorded if the PK sample is collected more than +/- 10 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF). All efforts will be made to collect Vital signs and ECGs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs and/or ECGs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[b] Hepatitis E testing only for participants who were in an area endemic for Hepatitis E in the past 90 days.

[c] Refer to Section 8.1 for additional information on drug, cotinine, and alcohol screening.

[d] Serum pregnancy test for women at Screening and urine testing at other visits that require pregnancy testing. Positive urine test should be confirmed by serum pregnancy test. Women of postmenopausal status should have FSH levels tested for confirmation at Screening.

[e] If a subject's clinical status changes or does not meet all inclusion/exclusion criteria before randomization, including applicable Day -1 assessments, the subject will not be randomized into the study.

[f] Enrollment can occur any time pre-dose. Randomization for Part C must occur in time to properly instruct the participant on either fasting or fed conditions.

[g] Each dosing day (Days 1, 4, and 7), subjects will receive a single PO dose of ALG-097558 (either Formulation 1 or Formulation 2 depending on randomization) in the morning. Depending on randomization schedule, the participant will either dosed in a fasted or fed condition. The fasted condition is defined as the

participant has fasted for ≥10 hours overnight until at least 4 hours post-dose; except as part of dosing, water may be consumed freely except between at least 1 hour prior to and at least1 hours after dosing. With dosing approximately 240 mL of water will be provided or fed. With the fed condition, subjects should consume a high-fat, high calorie meal that should start 30 minutes prior to administration of study drug and be consumed within 30 minutes or less before dosing and fast for at least 4 hours after dosing, as outlined in Section 1.2.3.

[h] A complete physical examination (including height at screening only and body weight measurement) will be performed at screening and Day 17. A symptom-directed physical examination will be performed at any time as indicated at all other visits.

[i] Single 12-lead ECGs will be collected during screening and at any time as depicted in table. Subjects must have been resting in the supine fashion for at least 5 minutes. All efforts will be made to collect ECGs as close to nominal time as possible. Protocol deviations will be recorded if ECGs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[j] Vital signs (oral temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate): will be measured in the supine position after resting for at least 5 minutes. On dosing days, vital sign measurements will be **collected within 2 hours** prior to treatment administration.
All efforts will be made to collect Vital signs as close to nominal time as possible. Protocol deviations will be recorded if Vital signs are collected more than +/- 15 minutes from nominal time. Exact time of collection will be noted on the source document and data collection record (e.g., CRF).

[k] To include a complete blood count with differential, comprehensive metabolic panel, coagulation and urinalysis see Table 4 in Section 8.3.5 for details. If urinalysis is positive, urine will need to be sent for microscopy sensitivity. Samples for serum chemistry will be obtained after a fast of at least 10 hours, however, in case of rechecks, participants may not have fasted for 10 hours prior to when the serum chemistry sample is taken. For Screening labs only, it will be recommended that the participant is requested to be in the fasted state but if the participant is not in the fasted state this will not be a protocol deviation.

[l] Blood samples will be collected for PK analysis of ALG-097558 and ALG-097730 metabolite on Day 1 predose, post dose at 0.25, 0.5, 1, 2 ,3, 4, 6, 8, and 12 hr., Day 2 (24 hours post dose), and Day 3 (48 hours post dose). Blood samples for ALG-097558 plasma PK analysis will also be collected on Day 4 Predose, post dose at 0.25, 0.5, 1, 2, 3, 4 ,6, 8, 12 hr., Day 5 (24 hours post dose), Day 6 (48 hours post dose), Day 7 Predose, post dose at, 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hr., Day 8 (24-hr post-dose), and Day 9 (48hour post-dose).

[m] In case of withdrawal from the study, subjects should return to the study site for a Withdrawal/Early Termination visit (same assessments as Day 9) as soon as possible, preferably within ≤72 hours.

Abbreviations: ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; PK=pharmacokinetics; PO=oral; QD=once daily.

2. INTRODUCTION

2.1 Purpose of Trial

2.1.1 Trial Rationale

Oral drugs with minimal or reduced concerns of complicated drug-drug interactions (DDIs) or significant contraindications but are still efficacious and safe for patients to use on their own in an outpatient setting, are urgently needed to manage and control the spread of COVID-19. The current standard of care treatment Paxlovid (nirmaltrevir/ritonavir) has significant DDIs, primarily due to ritonavir, and is contraindicated in a significant number of patients.

ALG-097558 is a highly potent SARS-CoV-2 protease inhibitor with pan-coronavirus antiviral activity that is being developed for the treatment of COVID-19. In the Phase 1 first-in-human study, ALG-097558 was well-tolerated and demonstrated a favorable pharmacokinetic profile that supports ritonavir-free dosing and absence of a clinically meaningful DDI with midazolam (a sensitive CYP3A4 substrate). The aim of this study is to further evaluate the DDI potential of ALG-097558 via co-administration with a P-gp substrate (dabigatran) and a CYP3A4 inhibitor/P-gp inhibitor (itraconazole). In addition, this study will evaluate the relative bioavailability and food effect of a new tablet formulation for ALG-097558.

2.1.2 Background

2.1.2.1 COVID-19

COVID-19 is a viral infection caused by the novel SARS-CoV-2 and its emerging variants. As of February 2024, more than 774 million confirmed cases of COVID-19 were reported worldwide, including 7 million deaths (WHO COVID-19 Dashboard). SARS-CoV-2 is highly transmissible and remains a major public health concern worldwide since it was first identified during an outbreak of respiratory illness in Wuhan, China in 2019 (WHO COVID-19 China).

The clinical spectrum of COVID-19 is variable with individuals infected with SARS-CoV-2 being asymptomatic or presenting with only a few nonspecific symptoms. Other infected patients can develop mild-to-moderate illness and recover without hospitalization. Still other patients may develop severe illness and require hospitalization or succumb to COVID-19. The most common symptoms associated with COVID-19 are fever, cough, fatigue, and loss of taste or smell (WHO COVID-19 Symptoms). For some patients, the infection may progress to cause more severe symptoms including pneumonia, acute respiratory distress syndrome, multi-organ dysfunction, and eventually death. The symptoms of COVID-19 may appear as soon as 2 days and up to 14 days after exposure to the virus (CDC 2022a); on average, the symptoms appear 5 to 6 days after infection with SARS-CoV-2 (WHO COVID-19 Symptoms).

Certain individuals are at higher risk for severe COVID-19 and adverse outcomes. The characteristics that put people at higher risk include individuals ≥60 years, anyone living in a nursing home or long-term care facility, or those with chronic medical conditions, such as chronic liver disease (e.g., hepatically impaired individuals) (NIH Table 2a 2022; CDC 2023). Smoking and underlying clinical conditions such as cardiovascular disease, diabetes, obesity, and

cancer are also considered high-risk factors (Kim et al. 2021; Thakur et al. 2021; Zheng et al. 2020).

Several factors continue to affect the ongoing presence of COVID-19 despite prior immunity from vaccination and/or prior infection:

- Emergence of new variants and subvariants that can evade the immune response generated from vaccination or from an earlier infection with the virus. With each new variant or subvariant, the transmissibility and/or virulence of the virus may increase.
- Certain individuals remain unvaccinated and/or unboosted for various reasons (e.g., lack of access, personal preference)
- Certain individuals (e.g., elderly, immunocompromised) remain more vulnerable to SARS-CoV-2 infection regardless of vaccination status.

Because COVID-19 is expected to have an ongoing presence around the world, treatments for established infection are needed in addition to the disease prevention provided with vaccines. An unmet need exists for effective and convenient treatments in an outpatient setting, particularly for high-risk patients, to prevent hospitalization and overwhelming hospital resources. Additionally, among low-risk patients, an effective treatment to reduce symptoms and viral shedding would allow patients to resume daily activities and slow the spread of SARS-CoV-2.

2.1.2.2 COVID-19 Treatments

Therapies for the treatment of patients with mild-to-moderate COVID-19 currently include small molecule direct-acting antivirals. With the emergence of variants of concern (e.g., omicron) containing mutations in the spike protein, anti-SARS-CoV-2 monoclonal antibodies are no longer recommended as a treatment option due to in vitro data showing reduced susceptibility to this drug class (NIH COVID-19 Treatment Guidelines; WHO Therapeutics and COVID-19).

Small molecule antiviral treatment options include the nucleoside/nucleotide inhibitors remdesivir (Veklury), and molnupiravir (Lagevrio) as well as the 3CLpro inhibitor Paxlovid™ (nirmatrelvir/ritonavir [RTV]). The use of remdesivir is limited by its requirement to be administered intravenously (FDA News Release 2020). Although administered orally, molnupiravir has demonstrated sub-optimal efficacy and is therefore only recommended when other options are not available (NIH Table 2a 2022) or feasible to use.

The current standard-of-care for non-hospitalized treatment of patients with mild-to-moderate COVID-19 is the oral antiviral agent Paxlovid (nirmatrelvir/RTV). Nirmatrelvir is a potent protease inhibitor specific for 3CLpro,'clearance, respectively; volume of distribution was moderate in rat and monkey and low in dog; and plasma half-life was 0.42-1.67 hours. ALG-097558 had low in vitro permeability, and an efflux ratio ≥16.2 due to interaction with P-glycoprotein (P-gp) as a substrate.

ALG-097730 was the major oxidative metabolite of ALG-097558 that was detected in several nonclinical species and demonstrated 4- to 30-fold reduced antiviral activity compared with ALG-097558. Following repeat administration for 14 days, the molar plasma exposures (AUC_{0-24}) of ALG-097730 were ≤34.0% and ≤21.7% relative to ALG-097558 in rat and dog, respectively.

Several formulations were tested in dogs, including the clinical solution formulation used in clinical Phase 1, several spray-dried dispersion (SDD) suspension formulations, and the SDD tablets. Plasma exposure in dogs was generally comparable across formulations; the dose-normalized plasma exposure with SDD tablets of 100 and 200 mg active pharmaceutical ingredient strength were 0.89- to 0.94-fold of the solution formulation.

Plasma protein binding was concentration dependent for ALG-097558 and independent of concentration for ALG-097730.

The DDI potential of both ALG-097558 and ALG-097730 was studied in vitro for a variety of CYPs and UGT1A1 enzymes and gut, hepatic, and renal transporters. At clinically relevant projected plasma exposures, the key DDI risk is expected to be due to CYP induction by ALG-097558 (CYP2B6 ≥1 μM and CYP3A4 ≥0.33 μM) and ALG-097730 (CYP2B6 and CYP3A4 ≥10 μM each); CYP3A inhibition (by ALG-097558 only); interaction of ALG-097558 and ALG-097730 as P-gp substrates; and ALG-097558 as a CYP3A substrate.

The first-in-human study (ALG-097558-701) studied doses up to 2000 mg in healthy volunteers as both as single and multiple doses. Single oral doses of up to 2000 mg (Parts 1 and 6) and multiple, Q12H doses of up to 800 mg for 7 days (Parts 2 and 3) in healthy volunteers were well tolerated. Across all subjects, no serious adverse events (SAEs), dose-limiting toxicities, or treatment-emergent adverse events (TEAEs) leading to premature study drug discontinuation were reported. There were no dose-responsive TEAEs reported with the possibility (based on limited data) of a dose responsive increase in diarrhea in participants administered higher (800 mg) doses of ALG-097558 for 7 days. Importantly, these diarrhea events were only observed in subjects receiving high doses (and volumes) of the ALG-097558 solution formulation, which contains polyethylene glycol, a known laxative, in 61.5% w/w ratio. Participants did not experience diarrhea events when receiving relatively high (600 mg Q12H×7 days) doses of ALG-097558 administered as a tablet formulation (i.e., no vehicle given), the formulation that will be evaluated in future clinical studies, including this study. All TEAEs were mild or moderate in severity. No clinically significant trends or findings were observed with respect to any TEAEs, laboratory results, physical examinations, vital signs, or ECGs.

The pharmacokinetics of ALG-097558 was defined in clinical Study ALG-097558-701 following both single and multiple doses. Following single doses of ALG-097558, absorption was rapid, with median time to reach maximum ALG-097558 concentration in plasma approximately 0.5-0.75 hours in fasted state and 2–3.4 hours in fed state. Plasma ALG-097558 exposure, as measured by AUC and C_{max}, increased in a broadly dose-proportional manner across the 100- to 2000-mg dose range. The terminal plasma half-life of ALG-097558 in humans following single doses was not dose dependent and was approximately 2-7 hours. The plasma metabolite ALG-097730 was approximately 28% to 41% of the parent ALG-097558. Following multiple daily dosing with the solution formulation, plasma ALG-097558 exposure reached steady-state approximately within 1-2 days with a significant decrease in plasma exposure (50%) noted only at Day 7 with the highest dose (800 mg Q12H) of ALG-097558. The relative oral bioavailability of the SDD tablet was ~102%, 158%, and 155% for C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$, respectively, compared with the solution formulation. In addition, a high-fat/high-calorie meal did not impact ALG-097558 plasma exposures of the tablet. Renal clearance was a minor elimination pathway with minimal urinary

excretion (<7% of total dose) at doses up to 1600 mg.Based on in vitro studies, ALG-097558 is an inducer of CYP3A4 at ≥0.33 μM and moderate inhibitor of CYP3A4. However, in the clinical DDI study with midazolam, ALG-097558 (and ALG-097730) was considered a weak inducer of CYP3A4. Therefore, sensitive CYP3A4 substrates will not require dose adjustment when co-administered with ALG-097558.

ALG-097558 is a selective, reversible, and potent inhibitor of the SARS-CoV-2 3CLpro with pan-coronavirus activity. Toxicologic effects noted in nonclinical studies at very high systemic exposures were reversible and monitorable. Human efficacious plasma exposures can be achieved without any need for RTV boosting at doses of 200 to 600 mg BID and still maintain a wide safety margin relative to the NOAEL from the repeat-dose toxicology studies. The risk- benefit profile, as determined by available nonclinical data and safety and PK data in healthy volunteers enrolled in Study ALG-097558-701, remains favorable and supportive of the continued evaluation of ALG-097558, including in subjects with COVID-19.

Study Parts A and B are designed to assess the perpetrator or victim DDI risk of ALG-097558 mediated by CYP/P-gp interactions in healthy adult subjects. As ALG-097558 is a substrate of CYP3A4 and P-gp transporters, any concomitant administration of an inhibitor or inducer drug may alter its exposures. The potential impact of itraconazole, a CYP3A potent inhibitor, on the ALG-097558 (victim) systemic exposure will be evaluated in Part A, while the potential impact of ALG-097558 (perpetrator) on dabigatran etexilate, a P-gp transporter substrate, will be investigated in Part B.

Study Part C is designed to study the bioavailability of a new formulation of the ALG-097558 tablet and the food effect on this tablet.

Additional information is in the ALG-097558 Investigator's Brochure.

2.2 Summary of Benefits and Risks

2.2.1 Benefit Summary

No benefit can be expected for healthy volunteers (HVs) who participate in Study 24-0026.

2.2.2 Risk Summary and Mitigation Strategy

2.2.2.1 Risk of Trial Intervention – ALG-097558

Safety data from Study ALG-097558-701 demonstrate that ALG-097558 dosing was generally well-tolerated in healthy volunteer subjects with single doses up to 2000 mg and multiple doses up to 800 mg Q12H for 7 days. A total of 90 healthy volunteers received a single oral dose ≤2000 mg, or multiple oral doses ≤800 mg (Q12H ×7 days) of ALG-097558 or placebo. No serious adverse events (SAEs), dose-limiting toxicities, or treatment-emergent adverse events (TEAEs) leading to premature study drug discontinuation were reported. All TEAEs were classified as severity Grade 1 (mild) or Grade 2 (moderate). There were no reported TEAEs of dysgeusia. The most common ALG-097558-related TEAE was diarrhea, recorded in 3 out of 15 subjects (20%) in multiple ascending dose part of the study, which involved multiple doses of 800 mg ALG-097558 Q12 h solution given in the fasted state. Of note, the ALG-097558 solution formulation contains PEG (a

known laxative). Other ALG-097558-related TEAEs included single cases of headache and somnolence. There were no clinically significant physical examination findings, or changes in laboratory variables, vital signs, or ECGs, in any study part.

Similarly, in nonclinical studies, ALG-097558 was well tolerated with no toxicologically relevant findings, including no target organ toxicity, in both rats up to 1000 mg/kg/day (highest feasible dose tested) and dogs up to 100 mg/kg/day (≥6.3-fold above the projected human efficacious range).

In dogs, at the very high dose of 500 mg/kg/day, ≥32-fold higher than the projected efficacious exposure range, ALG-097558 was not tolerated either as single or multiple doses with transient, monitorable changes in cardiovascular and respiratory parameters. In Study ALG-097558-701, no clinically relevant changes to hemodynamic or ECG parameters were observed. Considering the treatment duration for this drug of 5 (and not more than 10) days in humans and the wide margin between these observed effects and exposures in humans, as well as the safety data from Study ALG-097558-701, it is considered unlikely that these effects will be observed in future clinical studies. Nonetheless, potential related to cardiac dysfunction will continue to be monitored throughout clinical studies of ALG-097558.

A comprehensive panel of safety assessments including solicitation of AEs, laboratory investigations (e.g., hematology, serum chemistry, urinalysis, liver function tests), ECGs, vital signs and physical examinations will be performed at regular intervals throughout clinical studies of ALG-097558. ALG-097558 with or without DDI probes (dabigatran and itraconazole) will be administered to HVs under close medical supervision in a clinical pharmacology unit including this study. Finally, for the DDI evaluations (Parts A & B), additional eligibility criteria have been incorporated to exclude those at highest risk of the serious adverse reactions associated with dabigatran or itraconazole (Section 5.4) use. Common adverse events seen with itraconazole and dabigatran are located in Section 4.2.2 and 4.2.1.

For a detailed discussion of the risk profile of ALG-097558, refer to the ALG-097558 Investigator's Brochure.

2.2.2.2 Risk of Trial Procedures

There is a low risk associated with the trial procedures.

Confinement-The participants will be confined to the Clinical Research Unit during dosing to provide full access to care and minimize inconvenience associated with the study schedule.

Blood collection-redness, pain, bruising, bleeding, low hemoglobin levels, infection, lightheadedness, fainting, or blood clots (which may cause inflammation, swelling or pain).

ECG & Holter Monitoring- skin redness, itching, or soreness from sticker electrodes.

Oral Administration Risks-Unpleasant taste, irritation of the mouth and/or throat, discomfort from swallowing, cough, or vomiting

Fasting- dizziness, headache, stomach discomfort, and/or fainting

Privacy- loss of privacy and confidentiality are minimized by procedures.

2.2.3 Overall Benefit: Risk Conclusion

The overall risk profile for subjects participating in this study is considered to be low, particularly in light of monitorable and reversible toxicology findings for ALG-097558, the safety profile in humans in Study ALG-097558-701, and the planned intensive safety surveillance regimen, which should enable early detection of any emergent safety signals. Thus, the overall risk-benefit profile for ALG-097558 is considered acceptable.

3. TRIAL OBJECTIVES AND ENDPOINTS

3.1 Objectives and Associated Endpoints for Part A: DDI-Itraconazole

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
Evaluate the effect of a CYP3A4 inhibitor/P-gp inhibitor, itraconazole, on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	PK parameters of ALG-097558 and metabolite ALG-097730 in plasma, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following single dose administration alone or with co-administration of multiple dose itraconazole
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in HV participants when administered as monotherapy or in combination with itraconazole	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)
Exploratory †	

Evaluate the relationship between pharmacokinetics and safety	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data
Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, physical examinations, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK
Evaluate the relationship between the plasma ALG-097558 concentration and its effect on the QT interval on an ECG	2-sided upper 90% confidence interval of the placebo-adjusted change from baseline in QTc

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

3.2 Objectives and Associated Endpoints for Part B: DDI-Dabigatran

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
Evaluate the effect of multiple doses of ALG-097558 on the pharmacokinetics of a P-gp substrate, dabigatran	PK parameters of dabigatran (total) in plasma, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following single dose administration alone or with co-administration of multiple dose ALG-097558
Secondary	
Evaluate the safety and tolerability and PK of multiple doses of ALG-097558 in HV participants when administered alone or in combination with dabigatran	• Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis) • PK parameters of ALG-097558 and ALG-097730, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following administration of multiple dose ALG-097558

Exploratory †	
Evaluate the relationship between pharmacokinetics and safety Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, physical examinations, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

3.3 Objectives and Associated Endpoints for Part C: Relative Bioavailability and Food Effect

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
Evaluate the relative bioavailability of 2 different tablet formulations of ALG-097558 and effect of food on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	PK parameters of ALG-097558 and the metabolite ALG-097730 in plasma, including but not limited to $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, T_{lag}, C_{max}, and $t_{1/2}$, following single dose administration of Tablet Formulations 1 and 2 of ALG-097558 and following administration of a high-fat diet (Tablet Formulation 2)
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in HV participants	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)
Exploratory †	

• Evaluate the relationship between pharmacokinetics and safety	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data
• Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

4. TRIAL DESIGN

4.1 Description of Trial Design

This multi-part Phase 1 study consists of 3 parts, all conducted in healthy volunteers (HV). The drug-drug interaction (DDI) potential of ALG-097558 will be investigated in Part A: DDI-Itraconazole for the impact of a CYP3A4/P-gp inhibitor on the pharmacokinetics (PK) of ALG-097558 and Part B: DDI-Dabigatran for the impact of ALG-097558 on the PK of a P-gp substrate. In Part C: Relative Bioavailability and Food Effect, the relative bioavailability after single doses of Tablet Formulation 1 and Tablet Formulation 2 of ALG-097558 will be assessed; food effect for Tablet Formulation 2 following a high-fat diet will also be assessed. Participants will be assigned to receive single or multiple doses of ALG-097558 and single or multiple doses of one of the following concomitant drugs: itraconazole (Part A) or dabigatran etexilate (prodrug of dabigatran) (Part B). Note: dabigatran etexilate will be referred to as dabigatran for the remainder of the protocol. Tablet Formulation 1 (a spray-dried dispersion [SDD] tablet) will be used across Parts A-C, while Tablet Formulation 2 (conventional tablet) will be used for investigation of relative bioavailability in Part C only.

Each of these study parts will be enrolled sequentially.

Plasma samples from Parts A, B, and C will be assayed by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods for the determination of plasma ALG-097558, ALG-097730, and dabigatran concentrations.

The Protocol Schema can be found in Section 1.2.

The Schedule of Activities (SOA) can be found in Section 1.3.

Details of the PSRT oversight are found in Section 10.2.

4.1.1 Part A: DDI - Impact of Itraconazole (CYP3A4/P-gp inhibitor) on PK of ALG-097558

This part is a partially blind and partially placebo-controlled, fixed sequence, single group study being conducted in up to 12 adult HVs to investigate the effect of itraconazole, a CYP3A4/P-gp inhibitor on the pharmacokinetics of ALG-097558 (Figure 3). Eligible participants will receive a single PO dose of matching placebo for ALG-097558 on Day 1 in single blind fashion (subject blinded only). In order to facilitate single blind dosing, participants will be unaware of whether or not they are receiving ALG-097558 or placebo. Participants will then receive a single PO dose of 300 mg ALG-097558 on Day 2 in open label fashion, followed by a washout period of at least 2 days. Finally, participants will receive multiple PO doses of 200 mg itraconazole solution once daily (QD) on Days 4–10 in open label fashion, a single PO dose of matching placebo for ALG-097558 on Day 6 in single-blind fashion and a single PO dose of 300 mg ALG-097558 on Day 7 in open label fashion. Participants will be followed-up 14 days after administration of the last dose of study drug.

Administration of itraconazole and ALG-097558 will be in the fasted state at the same time on

dosing days. Administration of Tablet Formulation 1 (SDD tablet) of ALG-097558 will be used.

4.1.2 Part B: DDI - Impact of ALG-097558 on PK of Dabigatran (P-gp substrate)

This is an open-label, fixed sequence, single group study being conducted in up to 24 adult HVs to investigate the effect of ALG-097558 on the pharmacokinetics of a single dose of dabigatran, a P-glycoprotein (P-gp) substrate (Figure 2). Eligible participants will receive a single PO dose of 75 mg dabigatran on Day 1, followed by a washout period of at least 3 days. Participants will then receive multiple PO doses of 600 mg ALG-097558 Q12H on Days 4–5 (total of 3 doses) and a single PO dose of 75 mg dabigatran on Day 5. Participants will be followed up 10 days after administration of the last dose of study drug.

The administration of dabigatran and ALG-097558 will be in the fasted state at the same time on dosing days. Administration of Tablet Formulation 1 (SDD tablet) of ALG-097558 will be used.

4.1.3 Part C: Relative Bioavailability/Food Effect

This is an open-label, randomized, 3-arm crossover study being conducted in 15 adult HVs. There will be three dosing sequences of which two will compare PK of a single-dose of 600 mg Tablet Formulation 1 (SDD tablet) and Tablet Formulation 2 of ALG-097558 for relative bioavailability. Two sequences will measure the effect of food on the PK of the single-dose of 600 mg Tablet Formulation 2 (Figure 3).

On Day 1, eligible participants will receive one of three sequences either a single PO dose of 600 mg ALG-097558 (Tablet Formulation 1) in the fasted state, a single PO dose of 600 mg ALG-097558 (Tablet Formulation 2) in the fasted state, or a single PO dose of 600 mg ALG-097558 (Tablet Formulation 2) in the high-fat fed state followed by a washout period of 3 days. On Day 4, participants will receive a different dose from the three sequences, followed by a washout period of 3 days. On Day 7, participants will receive the final dose sequence. Participants will be followed-up 10 days after the administration of the last dose of study drug.

4.2 Rationale for Trial Design

Study Parts A and B are designed to assess the perpetrator or victim DDI risk of ALG-097558 mediated by CYP/P-gp interactions in healthy adult subjects. As ALG-097558 is a substrate of CYP3A4 and P-gp transporters, any concomitant administration of an inhibitor or inducer drug may alter its exposures. Section 4.2.2 and Section 4.2.1 discusses the probes selected for Part A and Part B, respectively. Of note, PK sampling of ALG-097558 is being collected in both DDI study parts to provide a more data to enhance the understanding of PK of ALG-097558 and its metabolite ALG-097730.

Part A (DDI-Itraconazole) will include placebo (for ALG-097558) dosing on Days 1 and 6 prior to dosing of subjects with a single dose of ALG-097558 on Days 2 and 7, respectively. Holter analysis during placebo dosing will facilitate calculation of a mean placebo-corrected change-from-baseline QTc in this study part and may enable pooling of such data with the mean placebo-corrected change-from-baseline QTc values derived from previous ALG-097558 studies. Given that the exposures of ALG-097558 are expected to increase in Part A, due to itraconazole CYP3A4 inhibition, inclusion of Holter data from this part will be important to include in downstream

concentration-QT analyses.

Co-administration of itraconazole + ALG-097558 in Part A is expected to increase ALG-097558 exposures approximately 10-fold. However, the exact extent of this drug-drug interaction and the resultant increases in ALG-097558 exposure will not be known until Part A study conduct is actually completed. Therefore, to account for the unlikely scenario where ALG-097558 exposures in Part A are higher than projected, Holter monitoring has been included in this study part for purposes of both safety oversight and to understand the impact such exposures may have on QTc. In order to avoid any potential confounding effect of pain/distress from needle/cannula insertion or blood draws on interpretation of QTc data, the procedures, including PK sampling, have been designed to be similar on dosing days where Holter monitoring is instituted – specifically, Day 1 (matching placebo for ALG-097558), Day 2 (ALG-097558), Day 6 (itraconazole + matching placebo for ALG-097558) and Day 7 (ALG-097558 + itraconazole).

4.2.1 Part A (DDI with Itraconazole)

Itraconazole is an azole antifungal approved for the treatment of onychomycosis. Itraconazole is a substrate and strong dual inhibitor of CYP3A4/P-glycoprotein (P-gp). Itraconazole is a commonly used DDI probe (strong inhibitor) in studies to evaluate an investigational drug as a CYP3A4 and P-gp substrate given its strong CYP3A4 and P-gp inhibition potential, low potential for QTc prolongation, well described safety profile and recognition by health authorities as a drug probe with strong CYP3A4 inhibition for DDI studies (Liu et al. 2015; EMA 2012; Itraconazole prescribing information). Common adverse reactions with itraconazole include upper respiratory tract infection, hepatic enzymes increased and hypoacusis. Itraconazole use has also been associated with cases of congestive heart failure and cardiac dysrhythmias/disease. Refer to the prescribing information for complete details on the safety profile of itraconazole.

Co-administration of itraconazole + ALG-097558 is expected to increase ALG-097558 exposures approximately 10-fold. However, the dose of ALG-097558 selected for this study part is one that, following co-administration with itraconazole, is projected to result in ALG-097558 exposures (AUC_{0-24}) that are ~2-fold lower than the maximum exposures defined in this protocol (dog NOAEL) (ALG-097558 Investigator Brochure). Although the likelihood of observing ALG-097558 exposures higher than the exposure limits is low, the exact extent of this drug-drug interaction and the resultant increases in ALG-097558 exposure will not be known until this study part is completed. Therefore, to account for the unlikely scenario where ALG- 097558 exposures in this study part are higher than projected, Holter monitoring has been included in this study part for purposes of both safety oversight and to understand the impact of such exposures on QTc. Holter analysis during placebo dosing will facilitate calculation of a mean placebo-corrected change-from-baseline QTc.

4.2.2 Part B (DDI with Dabigatran)

Dabigatran is a direct thrombin inhibitor approved for the treatment and prevention of blood clots to reduce the risk of stroke. Dabigatran is an in vitro and in vivo substrate of P-gp, well described safety profile and recognition by health authorities as a drug probe as a strong P-gp substrate for DDI studies. Common adverse reactions with dabigatran include gastrointestinal events and bleeding. Refer to the prescribing information for complete details on the safety profile of

dabigatran.

In this study, the potential impact of ALG-097558 (perpetrator) on dabigatran (victim) will be investigated.

4.2.3 Part C (Relative Bioavailability and Food Effect)

The study was designed to examine the effect of food on the single-dose pharmacokinetics of ALG-097558 (Part C) and provide relative bioavailability between two tablet formulations. Understanding the effect of food on the PK characteristics of ALG-097558 and the relative bioavailability with different formulations is essential for optimal dosing in subsequent clinical trials.

4.3 Access to Trial Intervention After End of Trial

Not applicable.

4.4 Start of Trial and End of Trial

The trial start date is the date that the trial is open for recruitment of participants at any clinical site. The date of first recruitment by signing an informed consent will be recorded.

The trial will be considered completed after the last participant's last visit has occurred; other study activities such as laboratory analysis, data management reconciliation, etc., may be ongoing. The trial may be subject to early termination as described in Section 10.5.

5. TRIAL POPULATION

5.1 Selection of Trial Population

The choice of using HVs in Parts 1 through 3 is standard in establishing the preliminary safety and PK profile of a non-oncology drug for formulation and DDI studies.

5.2 Rationale for Trial Population

See Section 2.1.1.

5.2.1 Inclusion of Vulnerable Participants

Not applicable.

5.2.2 Exclusion of Specific Populations

Because the effects on the fetus are not known, pregnant individuals will not be eligible for the trial. Participants of childbearing potential must utilize a highly effective method of contraception and will be required to have a negative serum pregnancy test at screening and negative urine pregnancy test at Day –1 prior to first dose. If urine pregnancy test is positive, it will be confirmed by a serum pregnancy test.

Children will not be included in this trial as presently there are no safety or efficacy data in adults.

Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

5.3 Inclusion Criteria

Participant Inclusion and Exclusion Criteria must be confirmed by a study clinician listed on the delegation log. No exemptions are granted on Participant Inclusion/Exclusion Criteria in DMID-sponsored trials.

In order to be eligible to participate in this trial, an individual must meet all of the following criteria:

1) Participant is able to read the written informed consent, states willingness to comply with all study procedures, and is anticipated to be available for all study visits.
2) Male or female adults between 18 and 65 years of age, inclusive.
3) Female participants must either be postmenopausal[1], permanently sterile[2], or of childbearing potential with acceptable birth control methods[3].

   [1]*Postmenopausal: a postmenopausal state is defined as no menses for at least 12 months without an alternative medical explanation, confirmed by a high follicle-stimulating hormone (FSH) level in the postmenopausal range at screening. NOTE: If there is a question about menopausal status in women on hormone replacement therapy (HRT), the woman will be required to use one of the protocol-defined non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.*

[2]*Permanently sterile: methods include hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral tubal occlusion.*

[3]*Women of childbearing potential (WOCBP): are only eligible if they and any non-sterile, male sexual partners agree to use protocol-defined highly effective (dependent or independent) contraceptive therapy, from the start of dosing until at least 90 days after the last dose. Acceptable method of contraception, including , hormonal contraceptives (e.g., oral, injectable, implantable, insertable, and transdermal patch), intrauterine device (with or without hormones), or double-barrier method (e.g., condom and spermicide) for 30 days prior to Screening, during the study, and for 90 days following the last administration of investigational product (IP). WOCBP must also agree to refrain from egg donations during the study and for at least 90 days following the last administration of IP.*

4) Male participants (who must agree to wear a condom with spermicide during sexual intercourse .[4]

   [4]*These contraceptive measures must be implemented, at a minimum, from the start of dosing until at least 90 days after the last dose. Male volunteers must agree not to donate sperm during the study and for 90 days following the last administration of IP.*

5) Participants must have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, extremes included.

6) Participants must be nonsmokers for at least 3 months prior to randomization/enrollment.

7) Participants must have a 12-lead electrocardiogram (ECG) that considered in an acceptable range for inclusion.[5]

   [5]*Criteria includes: heart rate between 40 and 100 beats per minute [bpm], extremes included; QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF) ≤450 ms (males) or ≤470 ms (females); QRS interval ≤120 ms; PR interval ≥110 to ≤220 ms; and in addition to fulfilling the above ECG criteria, ECG morphology must have no clinically significant abnormalities observed.*

   NOTE: Retesting of an apparently exclusionary ECG will be allowed once without prior approval from the Sponsor (following ECG collections described in Section 8.3.4). Participants with a retest ECG without clinically significant abnormalities as per this inclusion criterion may be included.

8) Participants must be deemed to be in good overall health by the Investigator on the basis of a medical evaluation[6] performed at Screening.

   [6]*Medical evaluation that includes the absence of any clinically significant abnormality and includes a physical examination, medical history, vital signs, and the results of blood chemistry, blood coagulation and hematology tests, and urinalysis.*

9) Subject must be willing and able to adhere to the Prohibited Medication requirements and Special Precautions as specified in the protocol (Section 6.8.1).

5.4 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this

trial:

1. Participants with any current or previous illness that, in the opinion of the Investigator, might confound the results of the study or pose risk in administering study drug to the subject.7

   [7]*Additionally illnesses that could prevent, limit, or confound the protocol specified assessments or study results' interpretation. This may include, but is not limited to, renal, cardiac, vascular, pulmonary, gastrointestinal, hepatologic, endocrine, neurologic, dermatologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances*.

2. Participants with a past history of cardiac arrhythmias, risk factors for Torsade de Pointes syndrome or clinical evidence at screening of significant or unstable cardiac disease.[8]

   [8]*Risk factors for Torsade de Pointes syndrome include hypokalemia and family history of long QT syndrome. Clinical evidence of cardiac disease include angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease, clinically significant ECG abnormalities, moderate to severe valvular disease or uncontrolled hypertension. Evidence of heart block or bundle branch block, inclusive of first-degree AV block and incomplete bundle branch block, on ECG is also exclusionary.*

3. Participants with a history of clinically significant drug allergy such as, but not limited to, sulfonamides or drug allergy witnessed in previous studies with experimental drugs.
4. Participants with a recent (within 1 year of randomization/enrollment) history of use of amphetamines, barbiturates, narcotic or other drugs of abuse/recreational drug use.[9]

   [9]*Use of these drugs under physician supervision (e.g., prescription narcotics for known pain disorder) are not exclusionary. Cannabis use is also not exclusionary unless detected at screening or Day -1 (Exclusion Criteria 7)*.

5. Excessive use of alcohol defined as regular consumption of ≥14 standard drinks/week (U.K. Guidance 2021).[10]

   [10]*For current definition of a standard drink, refer to the National Institute on Alcohol Abuse and Alcoholism website (NIAAA 2023).*

6. Unwilling to abstain from alcohol use for 1 week prior to start of study through end of study follow up.
7. Positive results for urine drug screen for barbiturates, opiates, amphetamines, methadone, cocaine, benzodiazepines, or cannabinoids, alcohol or cotinine test at screening and Day -1.
8. Participants with current viral infections.[11]

   [11]*Viral infections include the following:*

   - *Hepatitis A virus infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]).*

- *Hepatitis B infection defined as presence of HBsAg or HBV core antibody.*
- *Hepatitis C virus (HCV) infection (confirmed by HCV antibody and/or HCV RNA). Participants who have been treated and achieved sustained virologic response ≥6 months prior to screening with HCV RNA <LLOQ, target not detected, remain eligible.*
- *Hepatitis E virus: Anti-HEV IgM-positive and/or detectable HEV RNA level (only applies to participants with history of living or traveling to an HEV epidemic area within 90 days of screening).*
- *Human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection (confirmed by antibodies) at screening.*
- *Acute infection at the time of randomization/enrollment. If an acute infection is considered resolved prior to randomization/enrollment, the subject remains eligible.*

9. Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
10. Women who are breastfeeding or planning to breastfeed throughout the duration of the study.
11. Use of any medications (prescription and over-the-counter), vitamins, and/or herbal supplements[12] within 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study drug.

    [12]Exception of contraceptives and OTC doses of ibuprofen or acetaminophen of up to 3 doses per week

12. Use of prohibited medications (as described in Section 6.8.1) within 14 days (or 5 half-lives, whichever is longer) prior to the first dose of study drug.
13. Consumption of grapefruit, grapefruit juice, and Seville oranges within 7 days prior to first study drug administration.
14. Consumption of apple or orange juice, citrus fruits, vegetables from the mustard green family[13], and charbroiled meats within 7 days prior to first study drug administration.

    [13]Examples are kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard.

15. Consumption of any food or drink/beverage containing quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine) within 24 hours prior to study drug administration.
16. Participants having received an investigational agent within 30 days (or 5 half-lives, whichever is longer) prior to screening.
17. Participants currently participating in another clinical or medical interventional research study.
18. Participants with any ≥Grade 1 (DAIDS toxicity table v2.1) laboratory result that is considered clinically significant by the Investigator at screening. (Grade 1 laboratory result that is not clinically significant is allowed.)
19. Clinically significant abnormal vital signs[14] (evaluated in the supine position after at least 5 minutes of rest), confirmed with retesting after at least 5 minutes of additional rest.

[14] *Abnormal vital signs are based on the following criteria:*

- *Systolic blood pressure: <90 or >145 mmHg*
- *Diastolic blood pressure: <50 or >95 mmHg*
- *Pulse rate: <45 or >100 beats per minute*
- *Temperature: <36.1°C or >38.0°C*

20. Physical examination findings that are considered clinically significant per study principal investigator and/or study physician and likely to adversely impact study conduct and/or interpretation are exclusionary.
21. Participants who had major surgery (e.g., requiring general anesthesia) within 12 weeks before screening, planned during the study, or within 4 weeks after the last dose of study drug.[15]

    [15] *This includes participants who will not have fully recovered from surgery by the time the participant is expected to participate in the study. NOTE: Participants with planned surgical procedures to be conducted under local anesthesia may participate.*

22. Participants with renal dysfunction[16]

    [16] *Includes estimated creatinine clearance <80 mL/min/1.73 m^2 at screening or Day -1, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. CKD-EPI should not be corrected for participants of African ancestry.*

23. Participants with alanine aminotransferase (ALT) values >1.2× upper limit of normal (ULN) at screening or Day -1.
24. Participants who donated blood or plasma recently[17]

    [17] *Recently defined as within 56 days prior to screening, or loss of whole blood of more than 500 mL within 30 days prior to Day-1, or receipt of a blood transfusion within 1 year of study enrollment; receipt of Plasma 7 days prior to screening.*

25. Participant is an employee of the Sponsor, the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site.[18]

    [18] *This extends to family members of the employees or the Investigator.*

NOTE (for applicable inclusion and exclusion criteria): Retesting of abnormal laboratory or vital sign values that appear to be exclusionary will be allowed once without requiring prior approval from the Sponsor. Retesting must take place under appropriate conditions during the current or a subsequent (e.g., unscheduled) visit in the screening phase. Participants with a retest value that is no longer exclusionary may be included.

Isolated, asymptomatic laboratory abnormalities without apparent clinical correlates are not necessarily exclusionary.

<u>Additional Exclusion Criteria for Part A (Itraconazole DDI)</u>

1. Known hypersensitivity or previous AEs with itraconazole or other azole antifungals.

Additional Exclusion Criteria for Part B (Dabigatran DDI)

2. Participants with active or recent history of clinically significant bleeding, at risk of bleeding, or abnormal coagulation test (PT/INR or PTT/aPTT >ULN) result(s) at Screening.
3. Known hypersensitivity or previous AEs with dabigatran or other direct thrombin inhibitors.

5.5 Lifestyle Considerations

Participants will be required to be confined to the CRU during specific days of the study based on the part of the study that they are enrolled. See Schedule of Activities for details (Section 1.3).

5.5.1 Meals and Dietary Restrictions

During this trial, participants are asked to:

- Refrain from eating or drinking anything hot or cold within 10 minutes prior to taking oral temperature.
- Refrain from consuming food or drink containing poppy seeds within 72 hours of the screening visit and study Day –1 as this could cause a false positive urine drug screen result.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from 7 days before the first dosing until after the final dose.
- Refrain from consumption of apple or orange juice, citrus fruits, vegetables from mustard green family (kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard) and charbroiled meats from 7 days before the first dosing until after the final dose.
- Consumption of any food or drink/beverage containing quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine) within 24 hours prior to study drug administration.

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

During this trial, participants are asked to:

- Refrain from consumption of alcohol from 7 days prior to confinement through Follow-up or Early Termination Visit.
- Refrain from consumption of excessive caffeine. Caffeine intake should not exceed two 6-oz cups of coffee/day or two 12-oz containers of regular caffeinated soda/day for 48

hours prior to first study dose through completion of the last study visit or Early Termination visit.

- Refrain from tobacco use from 7 days prior to screening through Follow- up or Early Termination Visit.

5.5.3 Physical Activity

During this trial, participants are asked to:

- Abstain from strenuous exercise on dosing days for and 24 hours prior to confinement. Strenuous exercise defined as exercise that increases your heart rate and breathing making it difficult for you to speak in full sentences like running, cycling, singles tennis, or lifting heavy objects.

5.5.4 Other Activity

During this trial, participants are asked to:

- All females of childbearing age agree to using an acceptable method of contraception, including , hormonal contraceptives (e.g., oral, injectable, implantable, insertable, and transdermal patch), intrauterine device (with or without hormones), or double-barrier method (e.g., condom and spermicide) for 30 days prior to Screening, during the study, and for 90 days following the last administration of investigational product (IP).
- All male subjects agree to using a medically accepted contraceptive regimen during their participation in the clinical trial and for 90 days after last administration of the study drug. Acceptable methods of contraception for male participants enrolled in the study include condoms with spermicide or surgical sterilization (vasectomy) of participant. Surgical sterilization must have occurred at least 26 weeks before the Screening. Additionally, male subject must agree not to donate sperm during the study and for 90 days following the last administration of IP.
- After enrollment in this study (but before last visit), the participant should notify study staff of their intention to enroll in any other clinical study prior to enrollment in that study.

5.6 Screen Failures

After the screening evaluations have been completed, the investigator or designee will review the

inclusion/exclusion criteria and determine the participant’s eligibility for the trial.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) reason(s) for ineligibility, and protocol deviations (if applicable). Participants who are found to be ineligible will be told the reason for ineligibility.

Participants may be re-screened once due to a screening failure result as defined below.

During screening, if a physiologic parameter, *e.g.*, vital signs, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the

abnormality is the result of an acute, short-term, rapidly reversible condition (*e.g.*, stress, anxiety, or "white coat syndrome"). A physiologic parameter may be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (*e.g.*, inappropriate-sized blood pressure cuff).

A participant may be re-screened if there is a transient disease status (*e.g.*, participant complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (*e.g.*, a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).

A low creatinine value, low bilirubin, or a low ALT value are acceptable for trial inclusion as they are not considered to be clinically significant.

Participants will be provided the results of any abnormal clinical laboratory results and will be referred to their primary healthcare provider. Participants will not be provided with research laboratory results.

5.7 Strategies for Recruitment

Potential participants will learn about the trial via IRB-approved recruitment strategies, and local advertisements/flyers. Recruiting may begin with a brief IRB-approved telephone call between trial staff and the potential participant. Information about the trial will be presented to potential participants, and questions about their health and ability to comply with the trial visit schedule will be asked of potential participants to presumptively determine eligibility. Information about the participant may be recorded from interviews or medical records. Appointments will be made at the research clinic for potential participants who are interested in the trial for further screening procedures and additional protocol-specific information.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of Trial Intervention

ALG-097558

ALG-097558 is a selective, reversible, and potent inhibitor of the SARS-CoV-2 3CLpro with pan-coronavirus activity. Investigational product (IP) will be supplied by Aligos Therapeutics in two different formulations containing active pharmaceutical ingredient Tablet Formulation 1 a spray dried dispersion (SDD) tablet and as a second conventional tablet formulation containing active pharmaceutical ingredient (Tablet Formulation 2; Part C only).

Dabigatran Etexilate

Dabigatran is a direct thrombin inhibitor approved for the treatment and prevention of blood clots to reduce the risk of stroke. Dabigatran is an in vitro and in vivo substrate of P-gp, with a well described safety profile. Dabigatran is available as 75 mg capsules.

Itraconazole

Itraconazole is an azole antifungal approved for the treatment of onychomycosis. Itraconazole is a substrate and strong dual inhibitor of CYP3A4/P-glycoprotein (P-gp). Itraconazole is a commonly used DDI probe (strong inhibitor) in studies to evaluate an investigational drug as a CYP3A4 and P-gp substrate given its strong CYP3A4 and P-gp inhibition potential, low potential for QTc prolongation, and well described safety profile

Itraconazole Oral Solution is available in 150 mL amber glass bottles containing 10 mg of itraconazole per mL.

6.2 Rationale for Trial Intervention

The dose of ALG-097558 was selected based on the results of Study ALG-097558-701 and nonclinical data (ALG-097558 Investigator's Brochure). Additional information on the selection DDI probes are in Section 4.2.1 and 4.2.2.

6.3 Dosing and Administration

In study parts dosed in the fasted state, each dose will be administered with ~240 mL of water at ambient temperature following an overnight fast of at least 10 hours and subjects will continue to fast for at least 4 hours following dosing. Except as part of dosing, water may be consumed freely until 1 hour prior through1 hours after dosing. In the fed portion of Part C, the dose will be administered with ~240 mL of water at ambient temperature following a high-fat/high-calorie breakfast (following an overnight fast of at least 10 hours). The study subjects will start the recommended high-fat/high-calorie breakfast 30 minutes before administration of ALG-097558 and be encouraged to consume the meal entirely in 30 minutes or less. Subjects will continue to fast for at least 4 hours following dosing.

Part A: DDI-Itraconazole

Single dose PO administration (3 tablets) of matching placebo (SDD tablet) for ALG-097558 (Day 1), followed by single PO administration of 300 mg (3x100 mg) ALG-097558 Tablet Formulation 1 (SDD tablet) (Day 2) with a washout period of at least 2 days, followed by multiple PO doses of itraconazole 200 mg QD for 10 days (Days 4–13), single dose PO administration of matching placebo (SDD tablet) for ALG-097558 (Day 6), and single dose PO administration of 300 mg ALG-097558 Tablet Formulation 1 (SDD tablet) (Day 7).

- Screening: Up to 4 weeks
- Dosing (Matching placebo [SDD tablet] for ALG-097558): 1 day
- Dosing (ALG-097558 Tablet Formulation 1 [SDD tablet]) and Washout: 1 day and ≥2 days, respectively
- Dosing (ALG-097558 Tablet Formulation 1 [SDD tablet] + itraconazole + matching placebo (SDD tablet) for ALG-097558): 7 days itraconazole + single dose ALG-097558 Tablet Formulation 1 (SDD tablet) + single dose of matching placebo (SDD tablet)

Follow-up: 10 days

Part B: DDI-Dabigatran

Single dose PO administration of dabigatran 75 mg (Day 1), then a washout period of at least 3 days, followed by Q12H PO administration of 600 mg (six 100 mg tablets) ALG-097558 Tablet Formulation 1 (SDD tablet) for 2 days (Days 4–5; total of 3 doses) and single dose PO administration of dabigatran 75 mg (Day 5).

- Screening: Up to 4 weeks
- Dosing (dabigatran) and Washout: 1 day and ≥3 days, respectively
- Dosing (ALG-097558 Tablet Formulation 1 (SDD tablet) + dabigatran): 2 days ALG-097558 Tablet Formulation 1 (SDD tablet) + single dose dabigatran

Follow-up: 10 days

Part C: Relative Bioavailability/Food Effect

There are three treatments to be provided in Part C: single dose PO administration of ALG- 097558 (six 100 mg tablets) Tablet Formulation 1 (SDD tablet) in fasted state, single dose PO administration of ALG-097558 Tablet Formulation 2 (two 300 mg) in fasted state, and single dose PO administration of ALG-097558 Tablet Formulation 2 (two 300 mg tablets) in fed state. The order the participant receives these treatments will be randomized and each treatment period will be separated by a 3 day washout. See Section 1.2.3.

- Screening: Up to 4 weeks
- Dosing (Period 1) and Washout: 1 day and 3 days, respectively
- Dosing (Period 2) and Washout: 1 day and 3 days, respectively
- Dosing (Period 3) and Follow-up: 1 day and 10 days, respectively

6.4 Treatment of Overdose

A trial intervention overdose is when a participant receives more than the intended dose for their cohort by accident or error. If accidental overdose is suspected, the subject should be treated symptomatically. The medical monitor should be alerted to the situation.

6.5 Preparation, Handling, Storage, and Accountability

6.5.1 Formulation, Appearance, Packaging, and Labeling

ALG-097558

ALG-097558 will be supplied in two tablet formulations.

Tablet Formulation 1 being used in Parts A-C as 100-mg strength SDD tablets containing active pharmaceutical ingredient.

The tablet is oblong white to off-white, tablets containing ALG-097558 as a spray-dried intermediate. The spray-dried intermediate consists of the active and hypromellose acetate succinate (HPMCAS) as a polymer matrix. Standard tablet excipients, microcrystalline cellulose, mannitol, croscarmellose sodium, silicon dioxide, magnesium stearate are added to the spray- dried intermediate and compressed into tablets.

ALG-097558 100 mg tablets and placebo to match ALG-097558 100 mg tablets are packaged as 30-count tablets in 30cc HDPE containers with 1g silica gel desiccant in each container.

Tablet Formulation 2 used in Part C only as 300-mg strength convention tablet formulation contains active pharmaceutical ingredient and manufactured from a direct blend of active and tabletting excipients except for HPMCAS, followed by compression.

Tablet Formulation 2 (ALG-097558 [H]) tablets 300 mg are packaged as 30-count tablets in 60cc HDPE containers with 1g silica gel desiccant.

Dabigatran

Participants in Part B will also take a single PO dose of dabigatran (capsule) 75 mg. The 75 mg capsules have a cream-colored opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with “R75”. The color of the imprinting is black. The capsules will be stored at 25°C (77°F); excursions are permitted to 15°-30°C (59°-86°F). Once the bottle is opened, the product must be used within 4 months. The product should be stored in original packaging to protect from moisture.

Itraconazole

Participants in Part A will also take multiple 200 mg PO doses of itraconazole solution. Itraconazole Oral Solution is available in 150 mL amber glass bottles containing 10 mg of itraconazole per mL. As per the package insert, the itraconazole solution will be stored at or below 25°C (77°F) and will not be frozen.

Matching Placebo for Part A

Placebo to match ALG-097558 100mg tablets are oblong shaped, white tablets and are visually identical in appearance to the ALG-097558 100mg tablets. Placebo tablets utilize the same excipients as active 100mg tablets except for hypromellose acetate succinate polymer. Storage requirements will be the same as ALG-097558.

6.5.2 Handling and Storage of Trial Intervention

ALG-097558 tablets 100 mg and ALG-097558 (H) tablets 300 mg have a 30-month shelf life and 4-month shelf life, respectively, at the storage condition of 25±2°C/60±5% RH (labeled storage 15-25°C), with 30-day and 5-day excursions allowed for temperatures below 15°C or above 25°C up to 40°C, respectively. The drug product stability will be continuously monitored during the clinical study and the shelf life will be updated accordingly.

The temperature of the storage unit must be recorded daily (excluding non-business days and holidays, as applicable) and continuously monitored and recorded during the course of this trial per site-specific SOPs, and documentation will be maintained.

If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). Immediately notify the PI, study coordinator, DMID Clinical Project Manager, and the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov for further instructions before any additional study product is administered. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

Study product must be stored in a secure area with limited access (pharmacy staff only) and must be stored as above. Refer to MOP and study Pharmacy Manual.

6.5.3 Preparation

See the protocol-specific Pharmacy Manual for detailed information on the preparation, labeling, storage, and administration for each cohort.

6.5.4 Accountability

Product	Provider/Source
ALG-097558 Formulation 1 and Formulation 2	Aligos
Matching placebo for ALG-097558	Aligos
Dabigatran	site
Itraconazole	site

Study products from DMID Clinical Materials Services (DMID CMS) will be distributed to the clinical research site upon request and approval from DMID.

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway

Germantown, MD 20876

Accountability

The site PI is responsible for study product distribution, disposition, and accountability. The site PI may delegate to the site's research pharmacist responsibility for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). The sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the DMID- approved clinical monitoring plan (CMP).

Study product accountability records and dispensing logs should include, but are not limited to the following: DMID protocol number; drug name, dosage form, strength of the study product; manufacturer or other source; control, lot number or other identification number; expiration or retest date; date of receipt of the study product; quantity received from supplier; participant identification number; quantity dispensed as amount or dose per participant; balance of study product currently available; disposition of study product if not dispensed to a trial participant (e.g., disposed/destroyed or retuned to supplier as per protocol or protocol-specific MOP or as directed by DMID). Time of administration to the participant will be recorded on the appropriate case report form (CRF). All study product(s), including the amount of ALG-097558 and matching placebo, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.

Once all participant dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs).

Refer to the protocol-specific MOP for details on storing used study product(s).

Destruction

After the trial treatment period has ended or as appropriate over the course of the trial after study product accountability has been performed, disposition of unused and used ALG-097558 bottles should occur as noted:

- Unused and used ALG-097558 and matching placebo bottles:
    - Should be destroyed following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/SOP when destroying used and unused items.
    - A certificate of destruction or documentation of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

6.6 Participant Assignment, Randomization, and Blinding

6.6.1 Trial Intervention Assignment Procedures

Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

Human Use (ICH) guideline E6: GCP, screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the ClinSpark (Electronic Data Capture System).

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the participants will be enrolled.

6.6.2 Randomization

This is an open-label trial with sequential group enrollment for Part A and Part B and randomization will not be utilized for these parts. Part A has a nested single-blind dosing but no randomization. Part B is open-label dosing with no randomization. Part C participants will be randomized to receiving one of the three treatment sequences in different order (5 participants per arm) but there is no blinding of formulation being received. Participants will be randomized equally (1:1:1) into one of three treatment sequences

6.6.3 Blinding and Unblinding

This study will not be blinded outside Part A in which only the participants will be blinded to receiving placebo a day before the ALG-097558 dose on both Day 1 and Day 6. The placebo will be matching to the ALG-097558 dose in presentation and appearance. Primary endpoints for the study are dependent on PK concentrations which will not be influenced by the participant knowing what they are receiving.

6.7 Trial Intervention Compliance

Participants will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer the study product.

Each dose of study product will be administered by a licensed and trained member of the clinical research team, whose scope of practice includes drug administration, such as a clinical study nurse (LPN/RN), sub-investigator (NP/PA), or site Principal Investigator (MD). Further details are provided in the MOP.

Administration and date, time, and visual verification that the oral dose was swallowed will be documented on ClinSpark (the EDC system) and recorded on the appropriate CRF.

6.8 Concomitant Therapy

Concomitant medications to be reported in the CRF are prescription medications, over-the- counter medications, supplements, and vaccines received outside of the trial that are taken by the participant from the time the informed consent is signed through Follow-up.

Hormonal contraceptives taken by the participant in the 30 days prior to providing informed consent will be recorded on the appropriate CRF.

At each study visit following dosing, participants will be queried about new concomitant medications and changes to existing medications.

Medications that might interfere with the evaluation of the investigational product should not be used by the participant during the trial-reporting period (up to 65 days from study start) unless clinically indicated as part of the participant's health care.

In the event medical conditions dictate the use of medications, participants are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician, and inform the trial Investigator as soon as practical.

6.8.1 Prohibited Concomitant Therapy

Subjects are prohibited from using any prescribed or non-prescribed systemic or topical medications, including herbal medications, within 14 days of the first dose of IP with the exceptions in Section 6.8.2.

6.8.2 Permitted Concomitant Therapy

Permitted concomitant therapy are oral contraceptives for WOCBP and spermicide for men. If needed, nonsteroidal anti-inflammatory drugs are the preferred analgesics. If used, it should be limited to an ibuprofen (or equivalent) dose within over-the-counter dosing, wherever feasible. Although acetaminophen use is not encouraged due to its known risk of hepatotoxicity, if its use is required, the daily dose should not exceed 2 g/day.

6.8.3 Non-Research Standard of Care

If at any time during the inpatient facility stay, the participant develops illness requiring medical care that is beyond the care available in this facility, the participant will be transferred to a hospital capable of providing this level of care. The hospital and physicians accepting the participant for care will be informed of the participant's participation in this research trial so that the participant can be managed according to appropriate precautions per standard of care.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention

7.1.1 Participant Stopping Rules

The trial intervention will be discontinued in an individual if:

1. The participant becomes pregnant.
2. The participant met an exclusion criterion for participation in the trial (either newly developed or not previously recognized) that precludes further trial participation.
3. The participant has any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the participant.
4. The participant develops any medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the participant, interfere with the participant's successful completion of this trial, or interfere with the evaluation of responses.
5. Study product administration for any given participant may be stopped for SAEs, ≥ Grade 3 adverse events, ≥ Grade 3 safety laboratory abnormalities, or any other medical conditions that indicate to the Investigator that continued dosing is not in the best interest of the participant.
6. If signs and symptoms of a clinically significant hypersensitivity reaction occurs during or shortly after administration of the study products (oral), administration must be stopped and treated as needed.
7. QTcF of 500 ms OR increase of 60 ms above baseline value. Note: Two additional ECGs will be collected approximately 2 – 4 minutes apart to confirm the original measurement.
8. Any major bleeding in a participant in Part B.

Participants who have the study product stopped for safety related issues will not continue with dosing. In addition, participants who have an allergic reaction that is temporally associated with study product administration and the PI believes it to be related to study product will not receive any more study product.

In addition, a participant in this clinical study may discontinue study drug at their request for any reason. Every effort should be made to encourage participants to remain in the study for the duration of their planned outcome assessments. Participants should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Discontinuation from study drug does not mean discontinuation from the trial, and remaining trial procedures should be completed as indicated by the trial protocol. If a clinically significant finding

is identified (including but not limited to changes from baseline) after enrollment, the investigator or qualified designee listed on the form FDA 1572 will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data may be collected at the time of trial intervention discontinuation will include the following:

- Physical examination including weight
- ECG
- Vital signs
- Clinical laboratory (hematology, chemistry, coagulation, and urinalysis)
- AE monitoring
- Concomitant medication changes

7.1.2 Temporary Discontinuation or Interruption of Trial Intervention

Not applicable.

7.1.3 Rechallenge

Not applicable.

7.2 Participant Withdrawal from the Trial

Participants are free to withdraw from participation in the trial at any time upon request.

An investigator may withdraw a participant from the trial for the following reasons:

- Study non-compliance that in the opinion of the investigator poses an increased risk (*i.e.* missing safety labs) or compromises the validity of the data.
- Participant lost to follow-up

The reason for participant withdrawal from the trial, whether the decision was made by investigator or participant, and the extent of the withdrawal (*i.e.* whether participant withdrew from all components of research study or just the trial intervention) will be recorded on the Case Report Form (CRF).

Biospecimens collected for the current trial will still be used to analyze the trial endpoints.

7.2.1 Replacement of Participants

Participants who withdraw, or are withdrawn from this trial, or are lost to follow-up after signing the informed consent form (ICF) but before first treatment administration may be replaced. Any participant that has received any dose of IP and then subsequently withdraws for any reason will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for Follow-up scheduled visit and is unable to be contacted by the trial site staff after three attempts. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-mail, etc., made on separate occasions) will be made to locate or recall the participant, or at least to determine the participant's health status. These efforts will be documented in the participant's study file.

7.4 Trial Pause Rules

Further dosing and enrollment will be paused if any of the following criteria are met and confirmed:

- Occurrence of ≥1 SAE that is attributed (i.e., related, see Section 12.4) to study drug in any part of the trial, the study will be paused, OR
- ≥2 participants in the same part of the trial have to discontinue the study drug as defined by the participant stopping rules, that part of the trial will be paused OR
- ≥2 participants experience Grade ≥3 TEAEs of a similar nature (defined by MedDRA preferred terms) that are attributed (i.e., related, see Section 12.4) to study drug in any part of the trial, the study will be paused.

If the trial pause rule is met, an unscheduled safety analysis by the PSRT will be required for approval of further enrollment or continuation to other study parts.

8. TRIAL ASSESSMENTS AND PROCEDURES

Visits will consist of both inpatient (confinement) and outpatient based in-person clinic visits. If a participant is unable to present for a study visit within the specified window, it will be treated as a protocol deviation. Participants will be confined for a portion of the study length dependent on the part of study. Visit schedule for each part is in Section 1.3

Participants will be contacted by telephone to query for safety events as needed before the Follow-up visit. AEs that have occurred since the previous clinic visit or telephone call will be solicited. Based on the information collected, participants may be asked to return to the clinic for evaluation and assessments that could include vital signs, safety labs and physical exam.

8.1 Screening/Baseline Assessments and Procedures

Screening assessments can occur up to 28 days before the participant's first IP administration and may occur in one or two visits. At the first visit, and prior to any other trial-related activities, the participating site PI or appropriate sub-investigator will provide the participant with detailed trial information and will obtain written informed consent.

Some or all of the following assessments are performed during the screening visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history and demographics.
- Review pre-trial medications and therapies up to 30 days prior to the start of screening and record on the appropriate CRF. For the inclusion/exclusion criteria, review surgeries in the last 12 weeks, blood or plasma donations in the last 56 days, receipt of blood transfusion in the last year, and recreational drug use in the last year.
- Review of adult vaccinations, including any SARS-CoV-2 or other experimental coronavirus vaccines.
- Measure vital signs (HR, BP, respiratory rate, and oral temperature)
- Perform complete physical examination which will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system and height and weight for determination of BMI.
- Review of birth control history with female participants.
- Counsel all participants to use adequate birth control methods required during the trial to avoid pregnancy.
- Review inclusion and exclusion criteria.
- 12-lead electrocardiogram

- Obtain blood and urine for clinical screening laboratory evaluations. Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected for these evaluations is presented in Table 5.
    - Hematology – hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell counts with differentials
    - Chemistry (fasting or non-fasting) – albumin, alkaline phosphatase (ALP), ALT, AST, amylase, bicarbonate, bilirubin (total and direct), BUN, calcium, chloride, cholesterol (total, high-density lipoprotein, low-density lipoprotein),creatinine, creatine kinase, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, triglycerides, total protein, and uric acid
    - Coagulation – international normalized ratio, partial thromboplastin time, and prothrombin time
    - Urinalysis – color, appearance, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, protein, and urobilinogen
    - Serology – Hepatitis A, Hepatitis B surface antigen, Hepatitis C virus antibody, Hepatitis E immunoglobulin or RNA by PCR, HIV types 1 and 2 antigen/antibody (Hepatitis E immunoglobulin will only be for participants who visited an area the endemic with Hepatitis E in the past 90 days.)
    - FSH level from post-menopausal women
    - Serum pregnancy test (in female participants of childbearing potential)
    - Urine drug screen – methadone, amphetamines, barbiturates, cocaine, opiates, benzodiazepines, and cannabinoids
    - Urine for alcohol and cotinine, for recent alcohol and tobacco products consumption, respectively

The overall eligibility of the participant to participate in the trial will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the trial team.

Trial participants who qualify for inclusion will be contacted and scheduled for enrollment and first intervention within the window for enrollment.

Participants will be provided the results of abnormal clinical laboratory test values or abnormal clinical findings necessitating follow-up at the discretion of the participating site PI or appropriate sub-investigator.

8.2 Efficacy Assessments and Procedures

8.2.1 Efficacy Assessments

Not applicable.

8.2.2 Exploratory Efficacy Assessments

Not applicable.

8.3 Safety Assessments and Procedures

Trial procedures are specified in the SOA. A study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator, will be responsible for all trial-related medical decisions.

8.3.1 Medical History

A complete medical history will be obtained by interview of prospective participants at the screening visit. Prospective participants will be queried regarding a history of significant medical disorders of the head, ears, eyes, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

At all subsequent visits, an interim medical history will be obtained by interview of participants and any changes since the previous clinic visit or telephone call will be noted.

8.3.2 Physical Examination

- A comprehensive physical examination will be performed at the screening visit and timepoints specified in the SOA.
    - A full physical examination will include assessments of the following organs and organ systems: skin, HEENT, neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
    - Height and weight will be measured, and BMI calculated, at the screening visit only.
- A symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the SOA.
    - Interim or unscheduled physical examinations will be performed at the discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs or abnormal clinical laboratory test results.

8.3.3 Vital Signs

Vital sign measurements will include systolic and diastolic BP, HR, RR, and oral temperature. Vital signs will be measured at timepoints specified in the SOA. On dosing days, vital sign measurements will be collected within 2 hours prior to treatment administration. When vital signs collected subjects should be rested in a supine position for at least 5 minutes. Vital signs assessed on Day 1 prior to the first treatment will be considered as baseline. If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature. Vital signs will be graded according to the grading scale in Section 12.3.

8.3.4 Electrocardiograms

For Parts B and C, single 12-lead ECGs will be collected during screening and at specified times in the SOA. In Part A, triplicate ECGs are collected at Screening and on Days 1, 2, 6, and 7 before dosing with the ECGs taken at least 3 minutes apart within a 15 minute time period. For any ECG, subjects must have been resting in the supine fashion for at least 5 minutes. If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling. Triplicate ECGs will be conducted using the Holter monitoring when that is in use.

Safety endpoints, including change from baseline values (where appropriate), will be summarized by study visit using appropriate descriptive statistics. All collected data will be listed. ECG results will be categorized according to the potentially clinically significant abnormalities criteria (Section 15) and the categorization will be summarized as described in the SAP. Separate listings will be created for all extracted values over time for subjects with any post-baseline potentially clinically significant abnormal ECG results.

In Part A, Holter monitoring (12 lead) will be collected 2-hour (±15 minutes) predose (Day 1) through 24 hours post-Day 2 dose, on Day 3. The same will occur again 2-hour (±15 minutes) predose on Day 6 through 24 hours post-Day 7 dose on Day 8. Each continuous ECG recording will be performed for approximately 49.25 hours, starting 1.25-hour predose on Day 1 and on Day 6. Continuous ECGs (for the triplicate ECGs at these timepoints) will be extracted at a central ECG laboratory at the following time points, paired with PK determinations: at 3 time points within 1.25 hours prior to dosing (e.g., -1.25, -1.0, and -0.75 hours) and 0.25, 0.5, 1, 2, 3,

4, 6, 8, 12, and 24 hours postdose (Day 2 and Day 8). Subjects will be resting in a supine position for at least 5 minutes before and 5 minutes after each time point. If multiple assessments are scheduled for the same time point, procedures should be performed in the following order, where possible: ECG, vital signs, blood sampling.

8.3.5 Clinical Laboratory Assessments

- Fasting is required for at least 10 hours before collection of clinical safety laboratory evaluations. An attempt should be made to obtain screening laboratory evaluations in the fasted state but it will not be a protocol deviation if the participant has not fasted for this evaluation only.
- Serum pregnancy test will be performed locally by the site laboratory at the screening visit, and urine pregnancy test will be performed locally by the site laboratory within 24 hours prior to Day 1, and as needed at interim or unscheduled visits for all participants of childbearing potential. Results must be confirmed as negative prior to enrollment on Day 1. Positive urine pregnancy test will be confirmed by serum pregnancy test.
- Serology: Hepatitis A, Hepatitis B surface antigen, Hepatitis C virus antibody, Hepatitis E immunoglobulin M or RNA by PCR (*Hepatitis E screening only applies to participants with history of living or traveling to an HEV epidemic area within 90 days of screening)*, HIV types 1 and 2 antigen/antibody at the screening visit only.

- Urine drug screen for drugs of abuse (components per the standard panel at the site laboratory) at the Screening and Check-In (Day -1) visits. (Urine drug screen includes methadone, amphetamines, barbiturates, cocaine, opiates, benzodiazepines, and cannabinoids.)
- Urine for alcohol and cotinine, for recent alcohol and tobacco products consumption, respectively.
- Clinical safety laboratory evaluations (hematology, coagulation, urinalysis, and chemistry outlined in Table 4) collected at check-in (Day –1) will serve as the baseline and will be repeated as specified in the SOA.
    - Clinical safety laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected for clinical safety laboratory evaluations is presented in Table 5.
- Blood and urine will be collected at timepoints specified in the SOA.

Labs performed as part of a panel but not included among the clinical lab parameters specified above should not be reported in the database. However, if abnormal, the investigator should make a clinical decision about their clinical significance and, if clinically significant, they will be graded and reported per Section 8.4 (Adverse Events and Serious Adverse Events).

Table 4. Laboratory Parameters

Hematology		
Hematocrit	Platelet count	Reticulocytes
Hemoglobin	Red blood cell count	White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Serum chemistry		
Alanine aminotransferase	Calcium	Lipase
Albumin	Chloride	Magnesium
Alkaline phosphatase	Cholesterol (total, high-density lipoprotein, low-density lipoprotein)	Phosphate
Amylase	Creatine Kinase	Potassium
Aspartate aminotransferase	Creatinine	Protein, total
Blood Urea Nitrogen	Glucose	Sodium
Bicarbonate	hCG	Triglycerides
Bilirubin, direct and total	Lactate dehydrogenase	Uric acid
Coagulation		
Activate partial thromboplastin time	International normalized ratio	Prothrombin time
Urinalysis (by dipstick) [1]		
Appearance	Ketones	pH

Bilirubin	Leukocyte esterase	Protein
Color	Occult blood	Specific gravity
Glucose	Nitrates	Urobilinogen

[1] If urine dipstick is abnormal for blood, protein, glucose, or leukocyte esterase, urine microscopy will be performed (for WBC, RBC, bacteria and other cell counts), and the results will supersede those of the dipstick urinalysis.

Table 5. Blood Volumes by Laboratory Assessment

Laboratory Assessment	Blood Volume Required
Chemistry (lipase and hCG included)	About 8 mL
Serology/Hep	About 8 mL
Hematology	About 4 mL
Coagulation	About 3 mL
Maximum for Laboratory Assessments (at Screening)	About 23 mL

Note: Serology is only required at Screening

8.3.5.1 Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Conduct of the Trial

All abnormal clinical findings or clinically significant laboratory test values that occur post first dose will be considered AEs. The toxicity table from Division of AIDS (DAIDS) scale v2.1 (July 2017) should be used for grading. If a physiologic parameter, *e.g.*, vital sign or clinical laboratory value, is outside of the protocol- specified range (at screening), then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (*e.g.*, stress, anxiety or "white coat syndrome") or other source of error. A physiologic parameter may also be repeated (within the same study visit timepoint) if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (*e.g.*, inappropriate-sized BP cuff). If the repeat measure is within normal range, the clinical judgement of the site PI should be used. If clinical judgment still leaves doubt the PI may conduct a third measurement to break the tie. If the third measurement aligns with either the abnormal or repeat normal result, that outcome is considered definitive.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions of AE and SAE

Additional details and clarifications for AEs and SAEs are in Section 12.1 and Section 12.2.

8.4.1.1 Definition of Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding as

defined in Section 8.3.5), symptom, or disease temporally associated with the use of medicinal (investigational) product.

8.4.1.2 Definition of Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes (21 CFR 312.32 (a)):

- death
- a life-threatening adverse event*
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, etc.

* An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include grade 4 severity unless the adverse event might have caused death.

8.4.1.3 Definition of Serious and Unexpected Suspected Adverse Reactions (SUSAR)

A SUSAR is an adverse event that is considered serious, unexpected, and related to the study product or treatment.

An adverse event is serious if it meets the protocol definition of serious adverse event. An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the applicable product information (e.g., Investigator Brochure, package insert, and/or Summary of Product Characteristics); or the adverse event is not consistent with the risk information described in the protocol.

The Sponsor will be responsible for determining whether an adverse event is a SUSAR based on the nature, severity, or frequency of the event.

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

For this trial:

- Adverse events will be collected from signing informed consent through the end of the trial.
- Serious adverse events will be collected from signing informed consent through the end

of the trial.

Safety-related assessments are described in Section 8.3 and in the SOA and may lead to identification of AEs.

See Section 8.4.5 for follow-up of ongoing AEs/SAEs.

8.4.3 Identifying AEs and SAEs

The occurrence of an AE may come to the attention of study personnel during study visits, examinations, and interviews of a study participant presenting for medical care, or upon review by a study monitor.

8.4.4 Recording of AEs and SAEs

Any chronic medical diagnoses/conditions that are stable for the last 30 days (this includes no hospitalizations, ER, or urgent care visits, no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis/condition) that is present at the time the participant is screened will be considered as medical history and not reported as an AE. However, if the severity (*i.e.,* grade) of any baseline medical condition increases, or the participant develops any new condition after signing the informed consent, it should be recorded as an AE.

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis or AE term, if available. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

All AEs and SAEs will be captured on the appropriate eCRF. Information to be collected for AEs includes event term or description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and licensed to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship.

Additional details and clarifications for assessing severity and causality of AEs and SAEs are in Section 12.3 and Section 12.4.

8.4.5 Follow-up of AEs and SAEs

- All serious adverse events (SAEs) will be followed through resolution or until the site investigator deems the event to be chronic or stable.

- AEs will be followed through resolution or until the site investigator deems the event to be chronic or stable or has returned to baseline.

8.4.6 Reporting of SAEs

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group via the HiLIT electronic reporting system, fax, or email.

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com
SAE Electronic Reporting: www.dmidcroms.com
If HiLIT is not available, SAEs may be submitted via fax or email.

Any SAEs reported via the SAE Hot Line must be followed with an SAE form submitted via fax or email.

In addition to the SAE form, select SAE data fields must also be entered into the Data Coordinating Center (DCC) system in a timely manner. Please see the protocol-specific MOP for details regarding this procedure.

The SAE form will collect all relevant data concerning the SAE, including event term or description, date of onset, duration or date of resolution, severity, seriousness, outcome, any action taken with the study product, and relationship to each study product or an alternate etiology as assessed by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator. In addition, the investigator should provide relevant medical history, concomitant medications, laboratory or diagnostic results, details of any treatment for the SAE, and a narrative including all other pertinent medical information.

Other supporting documentation of the event may be attached to the SAE form and must not contain personal identifiable information (PII). Any additional information requested by the DMID Pharmacovigilance Group should be provided as soon as possible.

At any time after completion of the trial, if the site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

8.4.7 Regulatory Reporting Requirements for SAEs

Investigators must notify the Sponsor of all protocol-defined SAEs within 24 hours of site awareness. IRB is notified within 5 days of becoming aware of the event.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

The sponsor will report any SUSAR to the FDA in an IND safety report. DMID will report an AE as a suspected unexpected adverse event only if there is evidence to suggest a causal relationship between the trial intervention and the AE.

The Sponsor must ensure the event meets all three of the definitions:

1. Suspected adverse reaction.
2. Serious.
3. Unexpected.

Both seriousness and unexpectedness are important, but the event will be reported only if there is evidence to suggest a **causal relationship between the drug and the adverse event**, such as:

A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
B) One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug.
C) On review as an aggregate analysis when the occurrence is higher than the historical control.

DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

DMID will submit an IND safety report to the FDA and will notify all participating site Principal Investigators (*i.e.*, all Principal Investigators to whom the sponsor is providing drug under its IND(s) or under any Principal Investigator's IND(s) of potential serious risks from clinical studies or any other source, as soon as possible.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

8.4.9 Adverse Events of Special Interest (AESI)

Not applicable.

8.4.10 Disease-Related Events or Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.11 Unanticipated Problems

8.4.11.1 Definition of Unanticipated Problems (UP)

The Department of Health and Human Services OHRP considers **unanticipated problems (UPs)** involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; **and**
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents arising from noncompliance with trial procedures should be reported as protocol deviations (see Section 9.9). An incident that qualifies as both a UP and a protocol deviation should be reported as both.

8.4.11.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the trial sponsor, the reviewing Institutional Review Board (IRB), and to the Data Coordinating Center (DCC) <and the lead principal investigator (PI)>. The UP report will include the following information:

- Protocol identifying information: protocol number, PI's name;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other actions that have been taken or are proposed to resolve the UP or to prevent reoccurrence.

UPs that are SAEs should be reported according to the protocol-defined AE reporting guidelines (Section 8.4.6). UPs that are not SAEs should be reported to DMID within 3 days. UPs to be reported to the IRB must follow IRB reporting guidelines. If multiple timelines apply, use the most conservative timeline for reporting.

8.4.11.3 Reporting Unanticipated Problems to Participants

Participants will be informed of any UPs that will potentially influence their participation in this trial.

8.4.12 Reporting Events to Participants

Participants have the right to be informed of any new findings of AEs or SAEs that may affect their safety or influence their choice to participate or continue participating in the trial.

Any information provided to the participant will be blinded with respect to investigational treatment.

8.5 Pregnancy and Postpartum Information

8.5.1 Participants who Become Pregnant During the Trial

Pregnancy is not an AE. However, any pregnancy that occurs during trial participation (through Follow-up) should be reported to the sponsor on the appropriate CRF. Pregnancy should be followed to outcome. This follow-up will include pregnancy outcome (termination, pre-term birth, term birth), newborn outcome (live birth, fetal demise, stillbirth; presence of any congenital anomalies), and outcome over 1 year after birth. No in-person visits will be required for pregnancy outcome determination.

8.5.2 Participants Whose Partners Become Pregnant

The investigator will attempt to collect pregnancy information for a participant's partner, who becomes pregnant while the participant is in the trial. The partner will be provided with an ICF for this information, and it will be the same follow-up as outlined in Section 8.5.1.

8.6 Medical Device Product Complaints for Drug/Device Combination Products

Not applicable.

8.7 Pharmacokinetics

8.7.1 Pharmacokinetic Assessments

Full details of equipment and procedures for laboratory testing will be listed in the Laboratory Manual.

Blood samples for PK analysis will be collected at the scheduled times summarized in the SOA tables via an indwelling catheter and/or direct venipuncture. Saline or heparin flushes may be used to maintain viability of indwelling catheters. Additional information may be found in the Pharmacokinetic Sample Processing Manual.

All efforts will be made to obtain PK samples at the exact nominal time relative to dosing. Protocol deviations will be recorded if the PK sample is collected more than +/- 10 minutes from nominal time. Exact time of collection will be documented.noted on the source document and data collection record (e.g., CRF).

8.7.2 Blood Sample Collection for Pharmacokinetic Analysis

Part A – Impact of Itraconazole (CYP3A4/P-gp Inhibitor) on PK of ALG-097558

Approximately 45 blood samples will be drawn from each participant for PK analyses of ALG-097558 and ALG-097730 at the following time points (up to 3 mL at each sampling time).

Table 6. Part A: Timing of Blood Sample Collection and Volume

Timepoint →	Pre-Dose	0.25	0.5	1	2	3	4	6	8	12	24	48	72	Day total
Day 1	X	X	X	X	X	X	X	X	X	X				30 mL
Day 2	X	X	X	X	X	X	X	X	X	X				30 mL
Day 3											X			3 mL
Day 4												X		3 mL
Day 5														0 mL
Day 6	X	X	X	X	X	X	X	X	X	X				30 mL
Day 7	X	X	X	X	X	X	X	X	X	X				30 mL
Day 8											X			3 mL
Day 9												X		3 mL
Day 10													X	3 mL
Study Total Blood volume														135 mL

Part B DDI-Impact of ALG-097558 of PK of Dabigatran (P-gp Substrate)

Approximately 22 blood samples will be drawn from each participant for PK analyses of Dabigatran at the following time points (up to 3 mL at each sampling time).

Approximately 9 blood samples will be drawn from each participant for PK analyses of ALG-097558 and ALG-097730 at the following time points (up to 3 mL at each sampling time).

Table 7. Part B: Timing of Blood Sample Collection and Volume

Timepoint in hours →	Pre-Dose	1	2	4	6	8	12	24	36	48	72	Day total
Day 1	X	X	X	X	X	X	X					21 mL
Day 2								X	X			6 mL
Day 3										X		3 mL
Day 4											X	3 mL
Day 5	X A	X A	X A	X A	X A	X A	X A					42 mL
Day 6								X A	X			9 mL
Day 7										X		3 mL
Day 8											X	3 mL
Study Total Blood volume												90 mL

X= Dabigatran samples A=ALG-097558 and ALG-097730 samples

Part C – Relative Bioavailability and Food Effect

Approximately 36 blood samples will be drawn from each participant for PK of ALG-097558 and ALG-097730 analyses at the following time points (up to 3 mL at each sampling time).

Table 8. Part C: Timing of Blood Sample Collection and Volume

Timepoint	Pre-Dose	0.25	0.5	1	2	3	4	6	8	12	24	48	Day total
Day 1	X	X	X	X	X	X	X	X	X	X			30 mL
Day 2											X		3 mL
Day 3												X	3 mL
Day 4	X	X	X	X	X	X	X	X	X	X			30 mL
Day 5											X		3 mL
Day 6												X	3 mL
Day 7	X	X	X	X	X	X	X	X	X	X			30 mL
Day 8											X		3 mL
Day9												X	3 mL
Study Total Blood volume													108 mL

8.8 Genetics

Not applicable

8.9 Biomarkers

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

8.11 Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

The final clinical study report (CSR) will be completed when all primary and secondary safety, clinical, and pharmacokinetic (PK) endpoint data are available. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Any available results from the exploratory endpoints at the time of compilation of the final CSR may also be included. Additional exploratory endpoint results may be included in an addendum to the CSR, publication of manuscript(s), or other report.

No formal statistical safety or efficacy analysis will be performed for this study. However, summary tables of data will be provided, as appropriate, showing the number of subjects with nonmissing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentages for categorical variables. Data also will be listed as deemed appropriate.

Summary tables and data appendices will be created using the SAS® system. Further detailed explanation of outputs and statistical methods will be provided in the statistical analysis plan. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Missing data and outlier handling will be described in the Statistical Analysis Plan.

9.1 Analysis Sets

For purposes of analysis, the following populations are defined:

Population	**Description**
Enrolled analysis set	All participants who sign informed consent and are provided with an enrollment number.
Safety analysis set	Subjects which have received at least one dose of their allocated study intervention. Actual treatment assignment will be utilized for reporting.
Pharmacokinetic analysis set	All subjects in the safety analysis population who have sufficient PK data to estimate PK parameters.

9.2 Analyses Supporting Primary Objective(s)

Pharmacokinetic analysis will be performed using Pharsight® Knowledgebase Server™ and Phoenix® WinNonlin®, which are validated for bioequivalence/bioavailability studies by inVentiv. Inferential statistical analyses will be performed using SAS® according to FDA guidelines.

Individual and mean plasma concentration versus time curves will be presented for both linear and

semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of variation [CV (%)], minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented as well for the pharmacokinetic parameters.

9.2.1 Pharmacokinetic Parameter Analyzed from Plasma Samples

For Part A: DDI-Itraconazole

From the ALG-097558 and the metabolite ALG-097730 concentrations in plasma the following PK parameters will be calculated:

- AUC_{last}: area under the concentration-time curve from time zero to the last measurable concentration
- $AUC_{0\text{-}inf}$: area under the concentration-time curve from time zero to infinity (extrapolated)
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration
- C_{min}: minimum observed concentration
- C_0: initial concentration
- $t_{1/2}$: elimination half-life

For Part B: DDI-Dabigatran

From dabigatran concentrations in plasma the following PK parameters will be calculated for Day 1 (dabigatran alone) and Day 5 (dabigatran and ALG-097558):

- AUC_{last}: area under the concentration-time curve from time zero to the last measurable concentration
- $AUC_{0\text{-}inf}$: area under the concentration-time curve from time zero to infinity (extrapolated)
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration
- C_{min}: minimum observed concentration
- C_0: initial concentration
- $t_{1/2}$: elimination half-life

From the ALG-097558 and the metabolite ALG-097730 concentrations in plasma the following PK parameters will be calculated:

- AUC_{last}: area under the concentration-time curve from time zero to the last measurable concentration
- $AUC_{0\text{-}inf}$: area under the concentration-time curve from time zero to infinity (extrapolated)
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration
- C_{min}: minimum observed concentration

- C_0: initial concentration
- $t_{1/2}$: elimination half-life

For Part C: Relative Bioavailability and Food Effect

From the ALG-097558 and the metabolite ALG-097730 concentrations in plasma the following PK parameters will be calculated:

- AUC_{0-12}: area under the concentration-time curve from time zero to time 24 hours
- AUC_{0-24}: area under the concentration-time curve from time zero to time 24 hours
- AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
- AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated)
- T_{max}: time of observed C_{max}
- T_{lag}: time before the first concentration above the limit of quantification
- C_{max}: maximum observed concentration
- $t_{1/2}$: elimination half-life

9.2.2 Statistical Analyses of PK Data

Summary statistics will be used to describe the PK profile for each formulation and/or each dosing regimen/condition.

For evaluation of the potential food-effect in Part C, PK data (ln-transformed AUC_{0-t}, AUC_{0-inf}, C_{max}, and untransformed T_{max}) following a high-fat meal versus under fasting conditions will be compared by ANOVA using SAS®. The ratio (fed/fasting) and 90% geometric confidence interval will also be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Formulation changes will be evaluated similarly.

DDI in each Part A and Part B, will be evaluated using the geometric mean ratio (log- transformed) of the test treatment condition (i.e., combined-treatment condition) relative to the reference treatment condition (i.e., single-treatment condition) will be estimated with the 90% CIs calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Absence of a DDI will be concluded if the 90% CIs for the ratios of both C_{max} and AUC_{0-inf} are completely contained within the interval of 0.80 to 1.25. If there is unexpected difficulty in determining the $t_{1/2}$, AUC_{0-t} may be used in place of AUC_{0-inf}. The ratio comparisons of the PK parameters will be based on the following:

Part A: ALG-097558 plus itraconazole (test) versus ALG-097558 alone (reference).

Part B: ALG-097558 plus dabigatran (test) versus dabigatran alone (reference).

9.3 Analyses Supporting Secondary Objectives

Safety analyses are described in Section 9.5.

9.4 Analyses of Exploratory Objective(s)

Additional analysis may be performed. Please see the Statistical Analysis Plan (SAP) for details.

9.5 Safety Analyses

Safety analyses will be performed using the safety analysis set.

For all safety endpoints, descriptive statistics will be presented by Part and timepoint (where applicable). In summaries of change from Baseline safety variables, only subjects with both Baseline and post Baseline data will be included. No formal hypothesis tests will be performed for any safety endpoint. Determination of treatment-emergent AEs will be defined in the SAP.

Adverse event data will be coded using the Medical Dictionary for Regulatory Activities. The overall incidence of subjects having at least one AE will be summarized by Part and intervention, as well as condition. The incidence of TEAEs will be summarized by intervention, system organ class, and preferred term. Each subject will be counted only once per system organ class and preferred term. Additional summaries may be produced by severity and relationship.

In general, for safety analyses involving incidence reporting, including AEs, denominators may be adjusted to reflect the number of subjects in the safety analysis set which have received the reported intervention.

Safety endpoints, including maximum/minimum/worst change from baseline values (where appropriate), will be summarized using appropriate descriptive statistics. Separate listings may be created for all values over time for subjects with any post-baseline abnormal safety endpoints.

Vital signs and ECG results will be categorized according to the potentially clinically significant abnormalities criteria and the categorization will be summarized as described in the SAP. Separate listings will be created for subjects with any post-baseline potentially clinically significant abnormal vital sign/ECG result.

Laboratory results will be graded based on the grading scales defined in Section 12.3 and summarized as described in the SAP. Separate listings will be created for all values over time for subjects with any post-baseline abnormal laboratory results (all visits) and, if appropriate, for subjects with any post-baseline Grade ≥2 laboratory abnormalities (all visits). Graphs showing the actual and change from baseline may also be presented for selected laboratory parameters (e.g., liver function tests).

Physical exams will be listed as described in the SAP.

In the event a safety signal is detected, the relationship between study drug exposure(s) and various safety parameters including ECG changes, vital signs, and relevant laboratory parameters may be evaluated.

9.6 Other Analyses

Not applicable.

9.7 Interim Analyses

Not applicable.

9.8 Sample Size Determination

Up to approximately 51 participants are planned to be enrolled. No formal sample size calculation has been performed. The sample size chosen for each study part was based upon precedent set of by other trials of similar nature and are deemed sufficient to evaluate the study objectives for this early phase trial (Tornio 2019).

9.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the MOP, or GCP requirements.

The noncompliance may be either on the part of the participant, the investigator, or the trial site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All protocol deviations will be documented and entered into the data system.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID and IRB per the protocol deviation reporting procedures defined in the MOP. Protocol deviations must be sent to the IRB/IEC per their guidelines. The site principal investigator and personnel are responsible for knowing and adhering to their IRB requirements.

Changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the principles, laws, and regulations described in the Statement of Compliance.

Prior to the recruitment, screening and enrollment of participants, an OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment materials, and memory aids, handouts or surveys intended for the participants. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable.

Each institution engaged in this research will hold a current OHRP-approved Federal Wide Assurance (FWA).

Any amendments to the protocol or informed consent documents will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the trial. The participating site PI will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

DMID must receive the documentation that verifies IRB approval for this protocol, informed consent documents and associated documents, prior to the recruitment, screening and enrollment of subjects, and any IRB approvals for continuing review or amendments as required by the DMID.

A single IRB (sIRB) of record will be accountable for compliance with regulatory requirements for this multi-centered trial at domestic participating sites. A Reliance Agreement will be required between the sIRB and participating sites. The Reliance Agreement will set forth the specific responsibilities of the sIRB and each participating site. The participating sites will maintain essential documentation of sIRB and IRB reviews, approvals, and correspondence.

Participating sites must provide copies of essential documentation to the DMID or regulatory authorities upon request.

10.2 Committees

10.2.1 Protocol Safety Review Team

This study will use a Protocol Safety Review Team (PSRT), which is an advisory group internal to this trial that may be used for the protocol decision steps based on safety data and other factors that require the team's input and deliberation. PSRT members include the Principal Investigator (PI), the DMID Medical Monitor, and the DMID Medical Officer, with input provided from the DCC. Representatives from the drug developer may be included as non-voting members of the PSRT. The details of the PSRT process will be outlined in the PSRT charter.

10.2.2 Timing of Protocol Safety Review Team Review

10.2.2.1 Scheduled PSRT Review:

The scheduled PSRT review via email will be conducted as follows:

- Part A:

After the first three participants complete the active dosing period, an early safety assessment will be conducted. If any of these three participants does not complete the full active dosing, no replacement will be made, and PSRT will review the available safety data. If no safety concerns are identified, the remaining participants will proceed with their dosing. Once the active dosing period for the remaining participants is finished, the PSRT will review their data. Therefore, there will be two scheduled PSRT reviews for part A.

- Part B:

The PSRT review for Part B will follow the same procedure outlined in Part A.

- Part C:

PSRT will review the data once all participants have completed their active dosing as outlined in Section 4.1.3. There will not be an early safety assessment for part C. Thus, a single scheduled PSRT review will occur for part C.

10.2.2.2 Ad Hoc Meetings (Teleconference)

- When any pre-defined halting criteria are met.
- If any safety concerns are identified by either the DMID MM or the PI at any time during the study, the DMID MM will request an ad hoc PSRT meeting.

10.3 Informed Consent Process

Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any trial procedures are performed, informed consent will be obtained and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. Key information will include the purpose of the trial, the procedures and experimental aspects of the trial, trial interventions/products, probability for random assignment to treatment groups, risks and discomforts, the expected duration of the participant's participation in the trial, any expected benefits to the participant, and alternative treatments and procedures that may be available to the participant. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Participants will receive an explanation as to what happens if injury occurs, including whether any

compensation and any medical treatments are available, and, if so, what they consist of, or where further information may be obtained. Participants will be informed of the anticipated financial expenses, if any. They will be informed of whom to contact (*e.g.*, the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the trial for any reason at any time without penalty or loss of benefits to which the participant is otherwise entitled.

Participants will be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the participant is authorizing such access.

Participants will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved, and participants will be asked to read and review the consent form. Participants must sign the informed consent form prior to starting any trial procedures being done specifically for this trial. Once signed, a copy of the informed consent form will be given to the participant(s).

New information will be communicated by the site principal investigator to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented per IRB requirements, if necessary.

10.3.1 Consent for Genetic Testing

No human genetic testing will be conducted in this trial.

10.3.2 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other "primary" or "initial" activity, such as the data and samples collected in this protocol.

10.3.2.1 Samples for Secondary Research

Residual Research Sample

Any leftover Primary Research Sample after the laboratory testing specified in this protocol is completed will be stored for future studies on metabolites with the participant's consent. No

additional blood samples will be collected for these future studies. Specimens will be coded. Any future testing laboratory will not have access to the code and therefore will not be able to identify trial participants. Genetic testing on these samples will not be performed. The specifics of this testing will be in a separate protocol and will be reviewed by an IRB.

The participant's decision for secondary research can be changed at any time by notifying the study doctors or nurses in writing. If the participant changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

10.3.2.2 Data Sharing for Secondary Research

Data from this trial may be used for secondary research. All of the individual participant data collected during the trial will be made available after deidentification. This data will be available immediately following publication, with no end date. The data will be made available to researchers who provide a methodologically sound proposal. The data will be available for any purpose outlined in the approved proposal. Proposals should be directed to OBRAClinical@niaid.nih.gov. To gain access, data requestors will need to sign a data access agreement.

10.3.3 Research Related Injuries

For any potential research related injury, the site principal investigator or designee will assess the participant. The site principal investigator should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial. As needed, referrals to appropriate health care facilities will be provided to the participant.

No financial compensation will be provided by the NIAID, NIH, or the U.S. federal government to the participant, for any injury suffered due to participation in this trial.

The pharmaceutical collaborator, Aligos, has provided insurance for the study product.

10.3.3.1 PREP Act

The trial investigational product and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as ALG-097558.

The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on February 4, 2020.

The PREP Act also established the Health Resources and Services Administration (HRSA) Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the

CICP (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP website. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this trial, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

10.4 Data Protection

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples and genetic tests, and all other information generated during participation in the trial. No identifiable information concerning participants in the trial will be released to any unauthorized third party. Participant confidentiality will be maintained when trial results are published or discussed in conferences.

The trial monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All trial data and research specimens that leave the site (including any electronic transmission of data) will be coded.

As this research is funded by the NIH, it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality. By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this trial, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the participant from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not cover matters that must be legally reported, including child and elder abuse, sexual abuse, wanting to harm themselves or others, and certain infectious diseases that meet the criteria for reporting. In these cases, researchers may report information that would identify a participant without the participant's consent.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that the release is in compliance with applicable Federal regulations governing the protection of human subjects in research.

10.5 Early Site Closure or Trial Termination

This trial may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Regulatory authorities' determination
- Sponsor's determination

If the trial is prematurely terminated, the Principal Investigator (PI) will promptly inform trial participants and the Institutional Review Board (IRB) and regulatory authorities as applicable. Trial participants will be contacted, as applicable, and be informed of changes to study visit schedule. The PI will assure appropriate follow-up for the participants, as necessary.

The sponsor will notify applicable regulatory authorities of the trial termination.

11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

A quality tolerance limit (QTL) is a set of risks identified for this trial. A deviation from the set threshold during the conduct of the trial may indicate a systemic issue that could impact participant safety or the reliability of the trial results. The following are specified as QTL for this trial.

Table 9. Quality Tolerance Limits

Critical to Quality Factor	Parameter	Quality Tolerance Limit
Safety Reporting	The percentage of SAEs and AESIs not reported in the data system within 1 calendar day of site awareness.	Less than 80% of reportable events reported outside of the required reporting timeframe.
PK sample collection	The percentage of PK samples not collected per protocol required sample collection.	Less than 85% of the required PK sample collections required per protocol.
Data Integrity - Query Response	The percentage of queries not addressed by the site within 10 calendar days of issuance.	Less than 75% of queries responded to by the site within 10 days of query issuance.

11.2 Data Quality Assurance

11.2.1 Sponsor Responsibilities for Data Quality Assurance

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

11.2.1.1 Data Management

ClinSpark will be used for this trial for data management, quality review, analysis, and reporting of the trial data. ClinSpark is a 21 CFR Part 11-compliant cloud based data entry system including single-user password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Adverse events and medical history will be coded according to the MedDRA dictionary 27.1 or most current version.

Concomitant medications will be coded according to the WHODrug dictionary September 2024 or most current version.

At the end of the trial, a copy of all datasets including annotated case report forms (CRFs) and data

dictionary will be provided to DMID.

A separate Study Data Standardization Plan (SDSP) will be developed with the clinical study report (CSR) which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

11.2.1.2 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/amendment(s), International Council for Harmonisation, Good Clinical Practice, and with applicable regulatory requirement(s) and sponsor requirements. Monitoring for this trial will be performed by DMID or their agents. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, site trial intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, trial personnel, and all study documentation according to the DMID-approved site monitoring plan. Trial monitors will meet with site principal investigators to discuss any problems and outstanding issues and will document site visit findings and discussions.

11.2.2 Investigator Responsibilities for Data Quality Assurance

11.2.2.1 Data Collection

Data collection is the responsibility of the trial staff at the participating site under the supervision of the participating site PI. The participating site PI must maintain complete and accurate source documentation. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All paper source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Each staff member at a participating site who is responsible for data entry must maintain their own unique user ID and secure password.

Clinical research data from source documentation, including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will be entered by the participating site into eCRFs. See MOP for additional details.

At the end of the trial, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID per the requirements of the funding mechanism and agreements.

11.2.2.2 Site Quality Assurance and Quality Control

Each site participating in the conduct of a DMID-funded trial is responsible for integrating quality checks throughout the lifecycle of the protocol by developing, implementing, and evaluating a Clinical Quality Management Plan (CQMP). Quality activities are essential to the safety of participants, and the reliability of trial data. Quality management planning should be risk-based, commensurate with the risks associated with the research.

The CQMP will describe:

- Routine internal quality control (QC) and QA activities
    - for the purposes of measuring, documenting, and reporting trial conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
    - independent of sponsor site monitoring.
- A process for addressing data quality issues (*i.e.*, collecting, recording, and reporting findings in a timely manner); systemic issues (*i.e.*, protocol conduct, non-compliance, human subject protections), and implementation and evaluation of Corrective and Preventative Action Plan (CAPA) procedures.

11.3 Source Data

11.3.1 Definition of Source Data

Source data are all information, original records of clinical findings, observations, or other activities documented in a clinical trial necessary for the reconstruction and evaluation of the trial. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

For this trial, the eCRFs serve as the source documents for most of the data collected. Additional details can be found in the protocol-specific MOP.

Interview of participant is sufficient for obtaining medical history. Solicitation of medical records from the participant's primary care provider is not required.

Clinical measures such as clinical lab results and vital signs will be directly transferred from the clinical laboratory or device as direct data entry (DDE).

11.3.2 Data Capture Methods

Data will be captured and entered in real time into ClinSpark (EDC). All source data captured will be esource in ClinSpark, the only paper source will be the ICFs and Pharmacy records. Site staff will review ClinSpark for completeness and accuracy. Automatic quality checks are programmed in the EDC system to identify data discrepancies and resulting auto queries will be issued to the investigational site using an electronic query workflow within EDC. Designated site staff are required to respond to queries and make any necessary changes to the data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

A validated, electronic database will be deployed from an EDC platform system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the clinical database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, database closure, etc.) will be defined in advance together with a description of the personnel responsible for subject data entry. Clinical laboratory data will be transferred directly into the trial database from the clinical laboratory database.

11.3.3 Trial Record Retention

Trial related records, including the regulatory file, study product accountability records, consent forms, participant source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 3 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

11.4 Additional Considerations

11.4.1 Conflict of Interest Policy

Investigators will file appropriate financial disclosures prior to their involvement in this trial. The trial will adhere to relevant policies with regard to conflicts of interest.

11.4.2 Publication and Data Sharing Policy

11.4.2.1 Data Sharing Plan

This trial will be conducted in accordance with the following data sharing policies and regulations:

- As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov no later than 21 days after the enrollment of the first participant. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. As part of the result posting, a copy of this protocol and a copy of the Statistical Analysis Plan (if applicable) will be posted on ClinicalTrials.gov.

11.4.2.2 Publication

This trial will be conducted in accordance with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/) upon acceptance for publication.

12. APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1 Further Details and Clarifications on the AE Definition

AEs are to be graded according to the Division of AIDS (DAIDS) scale v2.1 (July 2017).

12.2 Further Details and Clarifications on the SAE Definition

Not applicable.

12.3 Severity

All AEs or SAEs will be assessed for severity according to the toxicity grading scales in Division of AIDS (DAIDS) scale v2.1 (July 2017). If the severity of any AE changes, the highest severity should be recorded.

- See the toxicity grading scales in the Division of AIDS (DAIDS) scale v2.1 (July 2017)

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Grade 1 (Mild): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.

Grade 2 (Moderate): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.

Grade 3 (Severe): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

Grade 4 (Potentially Life-Threatening): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

Additionally, when a laboratory result is assessed as an AE and cannot be graded using the DAIDS scale, the following flags will be used to characterize that abnormality.

Table 10. Flag Scale for Laboratory Abnormalities Assessed as an Adverse Event and Cannot be Graded Using the DAIDS Table

Grade	Abnormal High	Abnormal Low
1 (Mild)	>1 - <2 x ULN	<1 - ≥0.9 x LLN
2 (Moderate)	≥2 - <5 x ULN	<0.9 - >0.7 x LLN
3 (Severe)	≥5 - <10 x ULN	≤0.7 - >0.5 x LLN
4 (Potentially Life-Threatening)	≥10 x ULN	≤0.5 x LLN

LLN=lower limit of normal, ULN=upper limit of normal

12.4 Causality

For each reported adverse event or reaction, the Principal Investigator or designee must assess the relationship of the event to the study product using the following guideline:

Related – There is an association between the event and the administration of investigational study drug and/or DDI probe (as applicable), a plausible mechanism for the event to be related to the investigational study drug and/or DDI probe (as applicable) and causes other than the investigational study drug and/or DDI probe (as applicable) have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug and/or DDI probe (as applicable).

Not Related – The event is related to an etiology other than the investigational study drug and/or DDI probe (as applicable) (the alternative etiology must be documented in the study subject's medical record).

SAEs reported to the Sponsor will also be evaluated by the Sponsor for final causality determination and decision to report the event to regulatory authorities.

13. APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

Please refer to Sections 5.2.1 and 5.3 for guidance as to definitions of participants of childbearing (or non-childbearing) potential, acceptable contraception methods, and other considerations.

13.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the local site laboratories. The baseline result will determine eligibility for the primary analysis and the follow-up result will be used in evaluating the trial endpoints. Baseline result will be the last value collected before first dose of IP.

All plasma PK specimens will be shipped Syneos Health. Additional details can be found in the protocol-specific MOP.

Specimen preparation, handling, and storage will be done according to protocol-specific MOP.

13.3 Country/Region-Specific Differences

All trial sites are within the U.S.

13.4 Prior Protocol Amendments

This is the first amendment of the protocol and changes incorporated into this amendment are listed after the title page in this document.

14. APPENDIX: GLOSSARY OF TERMS

Table 11. Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	area under the concentration-time curve from time zero to time 24 hours
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
AUC_{0-t}	area under the concentration-time curve from time zero to the last non-zero concentration
AUC_{last}	area under the concentration-time curve from time zero to the last measurable concentration
BID	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
C_0	initial concentration
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
CRF	Case Report Form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support
CRU	Clinical research unit
CSR	Clinical Study Report
CYP	Cytochrome P450
DCC	Data Coordinating Center
DDE	Direct Data Entry
DDI	Drug-drug interaction
DMID	Division of Microbiology and Infectious Diseases

Abbreviation	Definition
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HV	Healthy volunteer
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent or Institutional Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug Application
INR	International normalize ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	intravenous
Ki	inhibition constant
LLOQ	Lower limit of quantitation
MAAE	Medically-Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MO	Medical Officer

Abbreviation	Definition
MOP	Manual of Procedures
N/A	Not applicable
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Condition
NOAEL	No observed adverse effect level
OHRP	Office for Human Research Protections
OTC	Over-the-counter
P-gp	Permeability-glycoprotein
PHI	Protected Health Information
PI	Principal Investigator
PIMMC	Potentially Immune-Mediated Medical Condition
PK	Pharmacokinetics
PO	oral
PREP	Public Readiness and Emergency Preparedness
PSRT	Protocol Safety Review Team
PT	Prothrombin time
PTT	Partial thromboplastin time
PVG	Pharmacovigilance Group
Q12H	Every 12 hours
QA	Quality Assurance
QC	Quality Control
QD	Once daily
QTc	QT interval corrected for heart rate
RTV	ritonavir
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDD	Spray-dried dispersion
SDSP	Study Data Standardization Plan
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	elimination half-life
TEAE	Treatment-emergent adverse events
T_{lag}	time before the first concentration above the limit of quantification
T_{max}	time of observed maximum concentration

Abbreviation	Definition
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization
WOCBP	Women of childbearing potential

15. APPENDIX: CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITES WITH ELECTROCARDIOGRAMS

Abnormality Code	**ECG Parameter**			
	HR bpm	**PR (ms)**	**QRS (ms)**	**QTc (ms)**
Actual Value				
Abnormally low	<45	Not applicable	–	–
Abnormally high	≥120	>220	≥120	–
Borderline prolonged QT	–	–	–	≥450 and ≤480
Prolonged QT	–	–	–	>480 and ≤500
Pathologically prolonged QT	–	–	–	>500
Change from Baseline				
Normal QTc change	–	–	–	ΔQTc <30
Borderline QTc change	–	–	–	ΔQTc ≥30 and ≤60
Abnormally high QTc change	–	–	–	ΔQTc >60

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