Aligos Therapeutics, Inc.
1 Corporate Drive, 2nd Floor
South San Francisco, CA 94080

Protocol No. ALG-097558-702

[redacted]

A Phase 1 Non-Randomized, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of ALG-097558 in Subjects with Moderate Hepatic Impairment and in Healthy Subjects with Normal Hepatic Function

Drug Name(s): ALG-097558

IND No. 163475

EudraCT No. *This is a Non-EU Study*

Date: 30 September 2024

Version: 3.0

Version History: 2.0, 14 August 2024
1.0, 20 June 2024

CONTACT INFORMATION

For up-to-date contact information, see Clinical Trial Master File: Emergency Contact Sheet.

All serious adverse events, and pregnancies and suspected pregnancies,[1] occurring from the time of consent up to 3 months after study drug administration is completed, regardless of relationship to study drug, must be reported to the Sponsor's designee within 24 hours of knowledge of the event.

Send all Serious Adverse Event Forms to:

[redacted]	
RTP Telephone contact:	[redacted]
Fax:	[redacted]

Sponsor's Medical Monitor:	[redacted]
Telephone contact:	[redacted]
SAE e-mail address:	[redacted]

Any serious adverse event, or adverse event that triggers subject discontinuation criteria (Section 5.8.4); pregnancy or suspected pregnancy must also be reported within 24 hours by telephone.

[1] See Sections 8.1.2, 8.1.3, and 8.1.4 for the definitions of *pretreatment adverse event, treatment-emergent adverse event, serious adverse event. Pregnancy in itself does not constitute an adverse event.*

TABLE OF CONTENTS

IN-TEXT TABLES

IN-TEXT FIGURES

LIST OF APPENDICES

ABBREVIATIONS

The following abbreviations and specialized terms are used in this protocol.

Term	Definition
3D-HAEC-ALI	three-dimensional human airway epithelial cell air-liquid-interphase
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BID	twice daily
BMI	body mass index
C_0	initial (fictive) or back-extrapolated plasma drug concentration at time zero following bolus intravenous injection
CICP	Countermeasures Injury Compensation Program
CKD-EPI	Kidney Disease Epidemiology Collaboration (measure of chronic maximum drug concentration in kidney)
C_{max}	maximum plasma drug concentration
C_{min}	minimum (trough) plasma drug concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
CRF	case report form
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DRM	data review meeting
EC_{90}, EC_{99}, $EC_{99.9}$	Concentration at which 90%, 99%, or 99.9% effectiveness is achieved
ECG	electrocardiogram
eCRF	electronic case report form
FSH	follicle-stimulating hormone
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human-*ether-à-go-go*-related gene
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	International Normalization Ratio
IRB	Institutional Review Board
MAD	multiple-ascending doses
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level

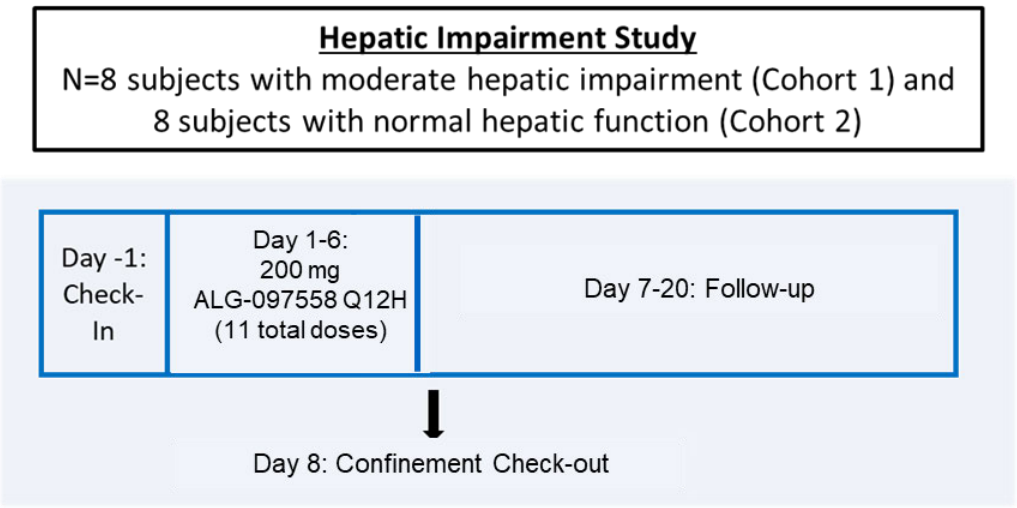
Term	Definition
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	oral
Q12H	twice daily (every 12 hours)
RTV	ritonavir
SAD	single-ascending doses
SAE	serious adverse event
SAP	statistical analysis plan
SDD	Spray-dried dispersion
SRC	Study Review Committee
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach the maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1.0 SYNOPSIS

A Phase 1 Non-Randomized, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of ALG-097558 in Subjects with Moderate Hepatic Impairment and in Healthy Subjects with Normal Hepatic Function

Protocol No.	ALG-097558-702
DMID Protocol No.	24-0001
Phase:	1
Study Drug(s):	ALG-097558
IND No.	163475
EudraCT No.	This is a Non-EU Study
Background Therapy:	None
Comparator:	None
Indication:	Coronavirus Disease 2019 (COVID-19)
Study Design:	**Overview** This is a Phase 1 non-randomized, open-label, multiple dose, parallel-group study of ALG-097558 in subjects with moderate hepatic impairment and subjects without hepatic impairment, matched for age, body weight and, to the extent possible, for gender. The primary purpose of this study is to characterize the effect of hepatic impairment on the plasma pharmacokinetics of ALG-097558 following administration of multiple, twice daily (Q12H) oral (PO) doses in approximately 16 subjects. Findings from this study will be used to develop dosing recommendations so that dose and/or dosing interval may be adjusted appropriately in the presence of hepatic disease. Eligible subjects will receive Q12H PO doses of 200 mg ALG-097558 (tablet) for 6 days for a total of 11 doses. Subjects will be followed up for 14 days after the administration of the last dose of study drug.

Synopsis Figure 1



	The Child-Pugh classification system (Table 1, Table 2) will be used to define the cohort of subjects with moderate hepatic impairment (Child-Pugh Class B). All subjects will be required to offer their own consent to participate in this study; as such, subjects with clinically active Grade 3 or Grade 4 encephalopathy (FDA 2003) will be excluded. Subjects with mild and severe hepatic impairment (Child-Pugh Class C, score: >9) will not be enrolled in this study; instead, pharmacokinetic (PK) modeling analyses, including population PK, physiologically based PK modeling, and exposure–response analysis will be performed to inform ALG-097558 PK estimates in subjects with mild and severe hepatic impairment. Enrollment of subjects with moderate hepatic impairment (Cohort 1) will initiate first. A planned Data Review Meeting will be conducted after at least 6 days of preliminary safety and PK data are available for 2 subjects in Cohort 1 to confirm or modify the ALG-097558 dose for the remaining Cohort 1 subjects and subsequent Cohort 2 subjects. Subjects with normal hepatic function (Cohort 2) will only be enrolled after all subjects in Cohort 1 complete the inpatient portion of the study. This staggered enrollment will help facilitate matching of the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; and, as much as practically possible, gender) between Cohorts 1 and 2. Reasonable efforts will be made to enroll an adequate number of subjects with Child-Pugh scores of 8 and 9 (1 to 3 subjects each) to ensure that the entire range of moderate hepatic impairment is represented. Administration of ALG-097558 will be in the fasted state. Refer to Section 6.0 for details on dose regimen administration with regard to food.

Synopsis Table 1. Study Cohorts Based on Hepatic Function

Cohort	Description	Child-Pugh Score	No. of Subjects [a]
1	Moderate hepatic impairment	Class B (7 to 9 points)	8
2	Normal hepatic function	Not Applicable	8

[a] Up to 3 additional subjects per cohort may be enrolled at the discretion of the SRC (see Section 3.4).

Synopsis Table 2. Assessment of Hepatic Impairment: Child-Pugh Scale

Assessment Parameters	Assigned Score for Observed Findings		
	1 point	2 point	3 point
Encephalopathy grade	0	1 or 2 (or suppressed with medication)	3 or 4
Ascites	Absent	Slight	Moderate
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, seconds prolonged	<4	4 to 6	>6

Objectives:

Primary

- To evaluate the comparative plasma pharmacokinetics of ALG-097558 and the metabolite, ALG-097730, following multiple doses in subjects with moderate hepatic impairment and matched healthy subjects with normal hepatic function.

Secondary

- To evaluate the safety and tolerability of multiple oral doses of ALG-097558 in subjects with hepatic impairment and in matched healthy subjects with normal hepatic function.

Exploratory

- To evaluate the relationship between PK and safety
- To evaluate the relationship between continuous measures of hepatic impairment, such as bilirubin, ALT, AST, prothrombin time, and serum albumin, and PK

Endpoints:

Primary

The primary endpoints are:

- PK parameters of total and unbound ALG-097558 and the metabolite ALG-097730 in plasma, including but not limited to $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$, following multiple oral doses

Secondary

The secondary endpoint is:

- Safety data, including treatment-emergent AEs (TEAEs), physical examinations, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology, liver function tests, and urinalysis)

	Exploratory • The exploratory endpoints may include, but are not limited to: • Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730, and safety data • Evaluate emergent safety, which may include AEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory results with PK • Evaluate liver function tests, including bilirubin, ALT, AST, prothrombin time and serum albumin, with PK • Change from baseline at various timepoints for various liver function tests, including bilirubin, ALT, AST, prothrombin time and serum albumin
Duration of Treatment and Study Period:	• Screening: Up to 28 days • Dosing Period: 6 days • Follow-up Period: 14 days
Dose Regimen and Duration:	Twice daily (Q12H) PO administration of 200 mg ALG-097558 (tablet) for 6 days for a total of 11 doses for all cohorts.
Number of Sites/Location:	A maximum of 7 sites are planned in the United States of America.
Sample Size:	Up to 22 adult subjects across Cohorts 1 and 2 will be enrolled.
Inclusion Criteria:	**Inclusion Criteria** 1) Male or female between 18 and 75 years of age, inclusive, at the Screening visit 2) Female subjects must either be not of childbearing potential, as defined below, OR, if they are a woman of childbearing potential (WOCBP), they are only eligible if they and any non-sterile, male sexual partners agree to use highly effective contraceptive therapy as defined in the Section 7.2.3. Woman not of childbearing potential defined as: a) Postmenopausal: A postmenopausal state is defined as no menses for at least 12 months without an alternative medical explanation. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. **OR** b) Permanently sterile:

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

3) Male subjects must agree to wear a condom during sexual intercourse and their female sexual partners must agree to use highly effective means of contraception. These contraceptive measures must be implemented, at a minimum, from the start of dosing until at least 90 days after the last dose.

   ***NOTE**: Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.*

4) Body mass index (BMI) of 17.5 to 40 kg/m2; and a total body weight >50 kg (110 lb).
5) Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6) Subjects who are willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

Additional **Inclusion Criteria for Subjects with Normal Hepatic Function (Cohort 2, *only)***

7) Good general health as defined by no clinically relevant abnormalities identified by:
   a) Medical history
   b) Vital signs in the following reference range:
      i) Systolic blood pressure: ≥90 to ≤150 mmHg
      ii) Diastolic blood pressure: ≥40 to ≤90 mmHg
      iii) Pulse rate: ≥40 to ≤100 beats per minute
8) Subjects must have a 12-lead electrocardiogram (ECG) that meets the following criteria:
   a) Heart rate between 40 and 100 beats per minute [bpm], extremes included;
   b) QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF) ≤450 ms (males) or ≤470 ms (females);
   c) QRS interval <120 ms;
   d) PR interval ≤220 ms;

e) 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. Subjects with a retest (single) ECG without clinically significant abnormalities as per this inclusion criterion may be included.*

9) Subjects must fit the demographic-matching criteria, including:
   a) A body weight that is ±15 kg of the median of Cohort 1, as provided by the Sponsor;
   b) An age that is ±10 years of the median of the Cohort 1, as provided by the Sponsor;
   c) **Attempts will be made** to ensure that the male-to-female distribution in Cohort 2 is comparable to that in the hepatic impairment Cohort 1
10) Normal hepatic function with no known or suspected hepatic impairment.

Additional **Inclusion Criteria for Subjects with Impaired Hepatic Function (Cohort 1, only)**

11) Absence of clinically significant abnormal screening medical history, physical examination, and clinical laboratory findings in the opinion of the Investigator; abnormal findings that are related to the subject's hepatic impairment and/or underlying condition which has resulted in their hepatic impairment are acceptable.
12) Subjects must have vital signs that meets the following criteria:
   a) Systolic blood pressure: ≥90 to ≤160 mmHg
   b) Diastolic blood pressure: ≥40 to ≤100 mmHg
   c) Pulse rate: ≥40 to ≤100 beats per minute
13) Subjects must have a 12-lead electrocardiogram (ECG) that meets the following criteria:
   a) Heart rate between 40 and 100 beats per minute [bpm], extremes included;
   b) QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF) ≤470 ms (males and females);
   c) QRS interval <120 ms;
   d) PR interval ≤220 ms;

	e) 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. Subjects with a retest (single) ECG without clinically significant abnormalities as per this inclusion criterion may be included.* 14) Subject satisfies the criteria for Class B of the Child-Pugh classification (Child Pugh Scores 7-9 points) within 28 days of study drug administration. 15) A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, FibroScan, computerized tomography scan, or magnetic resonance imaging (MRI). 16) Stable hepatic impairment, defined as no clinically significant change in disease status within 3 months prior to the Screening visit, as documented by the subject's recent medical history (e.g., no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or PT by more than 50%). If subjects do not have such records, 2 screening visits (at least 14 days apart) will be performed to demonstrate stability of the disease. 17) Stable concomitant medications (as defined in Section 6.9) for the management of an individual subject's medical history for at least 28 days. On a case-by-case basis, with input from the Sponsor, subjects receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.
Exclusion Criteria:	Any potential subject who meets any of the following criteria will be excluded from participating in the study. **Exclusion Criteria** 1. Subjects with any current or previous illness that, in the opinion of the Investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject or 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, endocrine, neurologic, dermatologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances. 2. Subjects with a past history or risk factors for *Torsade de Pointes* syndrome (e.g., family history of long QT Syndrome) or recent (within past 6 months) history or clinical evidence at screening of clinically significant or unstable cardiac disease such as: angina, congestive heart

	failure, myocardial infarction, diastolic dysfunction, arrhythmia, ECG abnormalities, moderate to severe valvular disease or uncontrolled hypertension. 3. Subjects 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. Subjects with a recent (within 1 year of randomization) history or current evidence of use of amphetamines, barbiturates, narcotic or other drugs of abuse/recreational drug use. Use of these drugs under physician supervision (e.g., prescription narcotics for known pain disorder) and cannabis use are not exclusionary. 5. Excessive use of alcohol defined as regular consumption of ≥14 standard drinks/week for women and ≥21 standard drinks/week for men (Chalasani et.al. 2018). For current definition of a standard drink, please refer to the National Institute on Alcohol Abuse and Alcoholism website (https://www.niaaa.nih.gov/what-standard-drink). 6. Unwilling to abstain from alcohol use for 48 hours prior to start of study through end of study follow up. a) Positive urine alcohol test at screening or Day -1 b) Positive pregnancy test at screening or Day -1 7. Subjects with current: a) Hepatitis B infection, defined as presence of HBsAg or HBV core antibody, unless, for Cohort 1, a subject meets the following criteria: i) On a stable HBV treatment regimen defined as currently receiving HBV nucleos(t)ide analogy (NA) therapy for ≥6 months prior to screening and have been on the same treatment regimen for ≥3 months at the time of screening; AND ii) Screening HBV DNA level <20 IU/mL; AND iii) NA treatment regimen with no suspected/known risk of drug-drug interactions with ALG-097558 b) HAV infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]). c) Hepatitis C virus (HCV) infection (confirmed by HCV antibody and HCV RNA). Subjects who have been treated and achieved sustained virologic response ≥6 months prior to screening with HCV RNA <LLOQ, target not detected, remain eligible. d) Anti-HEV IgM-positive and/or detectable HEV RNA level (only applies to subjects with history of living or traveling to an HEV epidemic area within 90 days of screening)

e) Human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection (confirmed by antibodies) at screening unless, for Cohort 1, a subject meets the following criteria:

i) On a stable HIV treatment regimen defined as currently receiving combination antiretroviral therapy (ART) for ≥6 months prior to screening and have been on the same treatment regimen for ≥3 months at the time of screening; AND

ii) Screening HIV-1 RNA level <LLOQ; AND

iii) CD4+ T cell count ≥350 cells/ml at screening and at least once during 12 months prior to screening; AND

iv) No history of AIDS-defining illness; AND

v) Combination ART regimen with no suspected/known risk of drug-drug interactions with ALG-097558

f) Acute infection, including SARS-CoV-2, at the time of randomization. If an acute infection is considered resolved prior to randomization, the subject remains eligible.

8. Subjects having received an unapproved investigational agent or vaccine within 4 weeks (or 5 half-lives, whichever is longer) prior to randomization
9. Use of prohibited medications (as described in Section 6.9) within 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study drug.
10. Subjects currently participating in another clinical or medical interventional research study.
11. Subjects who had major surgery (e.g., requiring general anesthesia) within 12 weeks before screening, or will not have fully recovered from surgery, or have surgery planned during the time the subject is expected to participate in the study, or within 4 weeks after the last dose of study drug.

    NOTE: *Subjects with planned surgical procedures to be conducted under local anesthesia may participate.*

Additional **Exclusion Criteria for Subjects with Normal Hepatic Function (Cohort 2, only)**

12. Estimated creatinine clearance <60 mL/min/1.73 m^2 at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula – Unless otherwise instructed by the SRC, CKD-EPI should not be corrected for subjects of African ancestry
13. The following laboratory values are exclusionary:

    a) Bilirubin (total, direct) >1.2× upper limit of normal (ULN) (unless Gilbert's is suspected), or

	b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >1.2×ULN c) Grade ≥1 Hemoglobin ***<u>Additional</u>* Exclusion Criteria for Subjects with Impaired Hepatic Function (Cohort 1, <u>only</u>)** 14. Subjects with advanced ascites (Grade 3) 15. Subjects with refractory encephalopathy as judged by the investigator. 16. Subjects with esophageal variceal bleeding within the past 6 months prior to screening. 17. Subjects with Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement. 18. Estimated creatinine clearance <60 mL/min/1.73 m^2 at screening, calculated by the CKD-EPI formula – Unless otherwise instructed by the SRC, CKD-EPI should not be corrected for subjects of African ancestry 19. The following laboratory values are exclusionary: a) ALT or AST level ≥5×ULN, or b) Serum sodium ≤125 mmol/L, or c) Platelets <50×10^9/L d) Grade ≥2 Hemoglobin ***NOTE:*** *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. Subjects with a retest value that is no longer exclusionary may be included.* *a. Vital signs can be repeated in the same or subsequent visit* *b. Laboratory tests should be repeated anytime within the screening window*
Dosage Form and Strength:	ALG-097558 will be supplied as tablets in 100 mg strengths.

2.0 BACKGROUND AND RATIONALE

2.1 Background Information on SARS-CoV-2

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 (HHS 2022). 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.

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, a viral protease that plays an essential role in viral replication. Nirmatrelvir is administered with RTV, a strong cytochrome P450 (CYP) 3A4 inhibitor and well-known pharmacokinetic (PK) boosting agent that increases and maintains the systemic concentration of nirmatrelvir, making Paxlovid an effective treatment against SARS-CoV-2. In a placebo-controlled trial with Paxlovid, patients in the Paxlovid group had an 88% relative risk reduction in COVID-19–related hospitalization or death from any cause by Day 28 among non-hospitalized adults at high risk for progression to severe disease (Hammond et al. 2022).

Despite its demonstrated efficacy, Paxlovid has significant drug-drug interactions (DDIs), primarily due to RTV, and is contraindicated in a significant number of patients, including those with severe hepatic impairment, who are receiving concomitant medications that cannot be stopped/modified (Paxlovid Fact Sheet 2022; NIH COVID-19 Treatment Guidelines). Because RTV is a strong CYP3A4 inhibitor, it may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4, potentially leading to toxicities. Ritonavir is also an inhibitor, inducer, and substrate of several other drug-metabolizing enzymes and/or drug transporters. Nirmatrelvir is a CYP3A4 substrate; therefore, concomitant administration of inducers of CYP3A4 may lead to decreases in Paxlovid concentrations, potentially reducing its effectiveness. A thorough review of a patient's concomitant medications, including prescription or nonprescription medications and herbal products is required before administering Paxlovid. Dose adjustments of Paxlovid or additional monitoring may be needed to ensure the effective and safe administration of the treatment and patient compliance.

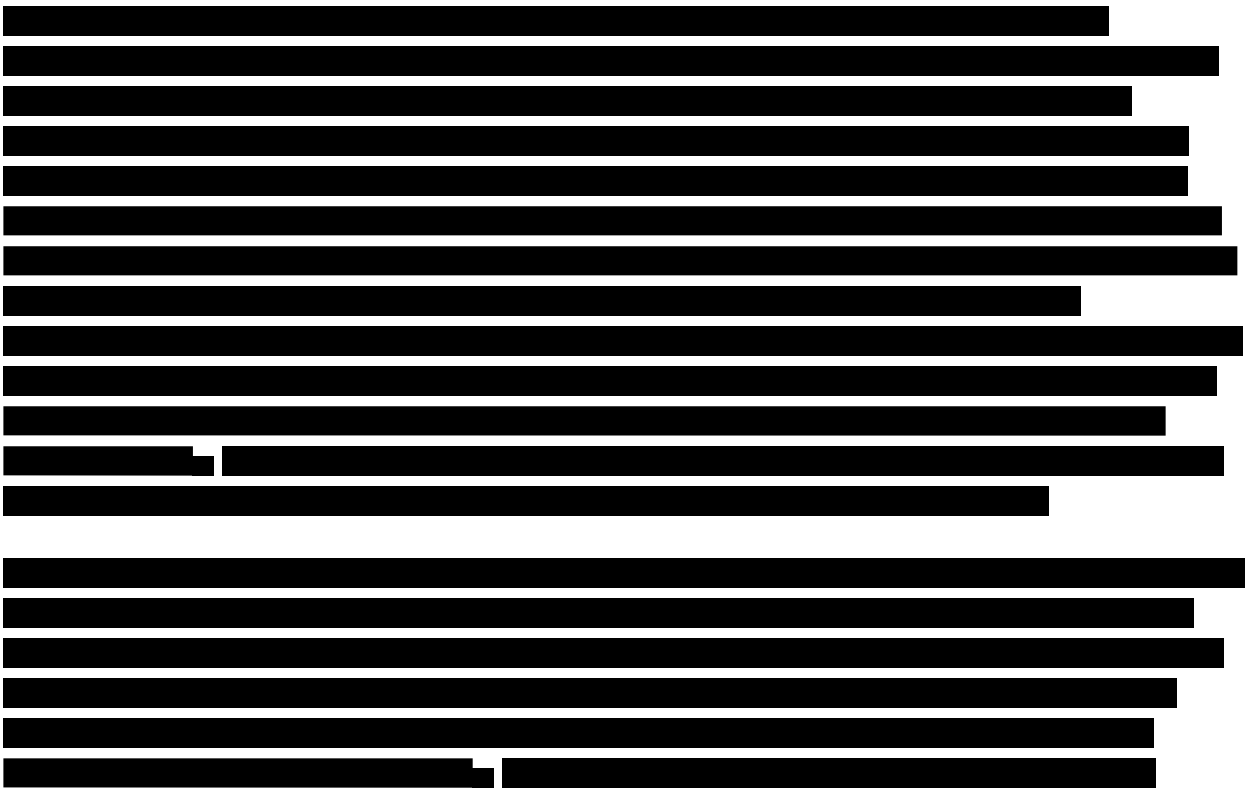
In this context, oral drugs with minimal or reduced concerns of complicated DDIs or significant contraindications, but are still efficacious and safe for patients to use on their own in an outpatient setting, are urgently needed to manage and control the spread of COVID-19.

2.2 Background on ALG-097558

2.2.1 Summary of Nonclinical Studies

ALG-097558 is a selective, reversible, and potent inhibitor of the SARS-CoV-2 3CLpro (half-maximal inhibitory concentration [IC_{50}] 0.22 nM, Ki 0.071 nM) in enzymatic assays. In cell-based experiments, ALG-097558 demonstrated pan-coronavirus activity with a narrow half-maximal effective concentration (EC_{50}) range of 7-40 nM against 8 different SARS-CoV-2 variants including Omicron, as well as other human coronaviruses. In three-dimensional human airway epithelial cell air-liquid-interphase (3D-HAEC-ALI) cultures, ALG-097558 inhibited the viral replication of SARS-CoV-2 B.1.1.7 (Alpha) with EC_{90}, EC_{99}, and $EC_{99.9}$ values of 1.8, 3.4, and 5.3 nM under serum-free conditions and of 33, 44, and 54 nM, respectively, in the presence of 40% human serum. Potent in vivo antiviral effects were noted using both therapeutic and prophylactic oral dosing in the hamster SARS-CoV-2 B.1.617.2 infection model.

ALG-097558 had good oral bioavailability in rat (19.2%) and dog (58.1%) with high and sustained plasma exposure obtained over the dose ranges studied. ALG-097558 is primarily metabolized by CYP3A4. ALG-097730, a major oxidative metabolite of ALG-097558 detected in several nonclinical species, demonstrated approximately 20-fold reduced antiviral activity compared with ALG-097558. ALG-097558 is primarily excreted via the biliary and fecal route in rats and dogs. As identified in the in vitro studies, the key DDI risk at clinically relevant ALG-097558 plasma exposures is expected to be due to CYP3A4 and CYP2B6 induction, CYP3A inhibition, and interaction as a P-gp and CYP3A substrate.



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 1. [redacted]

[redacted]

[redacted]

Additional details can be found in the Investigator's brochure.

2.2.2 Summary of Study ALG-097558 Clinical Experience

Study ALG-097558-701 (NCT05840952) is an ongoing Phase 1 first-in-human study defining the safety, tolerability, PK, and DDI potential of ALG-097558 in healthy volunteers for durations of up to 10 days. Parts 1 and 2 of the study is being conducted using SAD and MAD designs, including assessment of food effect. Subsequent parts of the study will be utilized to evaluate bioavailability of solid dosage forms (Part 6) and assess the perpetrator (using the drug probe midazolam) or victim (using the drug probes itraconazole and carbamazepine) DDI risk of ALG-097558 mediated by CYP/P-gp interactions (Parts 3-5). Parts 1 and 2 are double-blind, randomized, and placebo-controlled while Parts 3-6 are open-label. Parts 1 and 2 were conducted using a solution formulation. For Part 6, the relative bioavailability of a spray-dried dispersion (SDD) tablet (the same tablet that will be used in this study) compared with solution was evaluated, and the effect of high-fat food on ALG-097558 pharmacokinetics was evaluated following administration with the SDD tablet. Part 3 was subsequently conducted using the SDD tablet. Parts 4 and 5 are not planned to be conducted. Preliminary safety data as of 15 May 2024 from Study ALG-097558-701 are summarized in the following sections. As of 15 May 2024, study Parts 1, 2 and 6 are complete with data unblinded. The dosing period and post-treatment follow-up of open-label Part 3 are complete but the data remain preliminary.

In Part 1 (SAD), across 6 cohorts of healthy volunteers (n=51), a single oral dose of ALG-097558 or placebo were administered. In Cohorts 1-5 (n=8 each), 6 subjects were randomly assigned to receive ALG-097558 and 2 subjects to receive placebo. In Cohort 6 (n=11), 9 subjects were randomly assigned to receive ALG-097558 and 2 subjects to receive placebo. The following doses were evaluated: 100 mg for Cohort 1, 200 mg for Cohort 2, 400 mg for Cohort 3, 800 mg for Cohort 4, 1600 mg for Cohort 5 and 2000 mg for Cohort 6 in a fasted (Cohorts 1, 3 and 4), fasted and fed (Cohort 2), or fed (Cohorts 5 and 6) state.

In Part 2 (MAD), across 2 cohorts of healthy volunteers (n=15), oral twice daily doses (Q12H) for 7 days of ALG-097558 or placebo (randomized 3:1 ALG-097558:placebo) in Cohorts 1 (350 mg; n=8) and 2 (800 mg; n=7) were evaluated.

In Part 3 (midazolam DDI), in one cohort (n=12) of healthy volunteers, oral twice daily (Q12H) doses of 600 mg ALG-097558 were administered for 7 days after a single PO dose of 2 mg

midazolam and a washout period of 3 days. A second single PO dose of 2 mg midazolam was administered on the 5th day of ALG-097558 dosing.

In Part 6, in one cohort (n=12) of healthy volunteers, 3 single doses of 600 mg ALG-097558 were evaluated in a fixed sequence (600 mg solution, fasted; 600 mg tablet formulation, fasted; 600 mg tablet formulation, fed), all separated by a washout period of 3 days.

2.2.2.1 Safety Results

To date, a total of 90 healthy volunteers have 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. Based on preliminary blinded safety data, the doses were well-tolerated, with only mild (Grade 1) to moderate (Grade 2) TEAEs and no clinically concerning laboratory abnormalities, ECGs, vital signs or physical examination findings.

The details of Study ALG-097558-701 clinical safety data are provided in Investigator's Brochure.

2.2.2.2 Pharmacokinetic Results

The pharmacokinetics of ALG-097558 was defined in clinical Study ALG-097558-701 following both single and multiple doses. The mean plasma–time concentration plots for ALG-097558 following a single dose of 100 to 2000 mg ALG-097558 oral administration in either fasted or fed state in Study ALG-097558-701 Part 1 are shown in Figure 1 and the PK parameters are summarized in Table 2 and Table 3. 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_{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 the ALG-097558 plasma pharmacokinetics from Study ALG-097558-701, at doses ≥200 mg BID ALG-097558 SDD tablet are projected to maintain C_{trough} at least 4× EC_{90} (serum-

shifted EC_{90} of 17.8 ng/mL) level based on HAE ALI assay, while doses ≥400 mg BID are projected to maintain C_{trough} at least 5×$EC_{99.9}$ (serum-shifted $EC_{99.9}$ of 29.1 ng/mL) level, which are predicted to be sufficient for antiviral efficacy. Reduction in ALG-097558 exposure was noted on Day 7 of multiple dosing with the solution formulation, based on C_{trough} ALG-097558 concentrations. However, following administrations of either 800 mg Q12H solution of ALG-097558 or 600 mg Q12H SDD tablets of ALG-097558 (to be used for future clinical trials) for 5 days (10 total doses), the therapeutic dosing period expected for clinical trials of COVID-19 patients, steady-state ALG-097558 plasma concentrations were maintained between Day 1 and Day 5 above the 5-fold serum-shifted $EC_{99.9}$ for antiviral efficacy for the entire treatment period. Therefore, the therapeutic range is considered to be between 200 to 600 mg BID.

Based on in vitro studies, ALG-097558 is an inducer for 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, no adjustments are necessary for concomitant medications that are sensitive CYP3A4 substrates when co-administered with ALG-097558 in clinical trials. Co-administration of ALG-097558 and sensitive CYP3A4 substrates with narrow therapeutic index will also be allowed but should be done with caution, including monitoring for potential loss of efficacy.

Additionally, ALG-097558 is a substrate of CYP3A4 and both ALG-097558 and ALG-097730 are P-gp substrates. Therefore, any concomitant administration of an inhibitor or inducer of CYP3A4 or P-gp may alter the exposures. ALG-097558 has low inhibition potential of CYP2C8 and P-gp, and induction potential for CYP2B6 (≥1 μM). Therefore, as a precaution, until clinically evaluated, strong CYP3A4/P-gp inhibitors and inducers, and sensitive CYP2C8 and CYP2B6 substrates, will be prohibited in clinical studies.

ALG-097730, the major metabolite, has a reduced induction potential for CYP3A4 and CYP2B6 enzymes (≥10 μM) compared with ALG-097558 in the in vitro studies and is not expected to have any meaningful contribution to DDI at clinically relevant exposures.

Figure 1. **Mean (SD) Plasma Concentration-Time Profiles of ALG-097558 and ALG-097730 Following a Single Oral Dose of ALG-097558 in Study ALG-097558-701 (log-linear scale)**

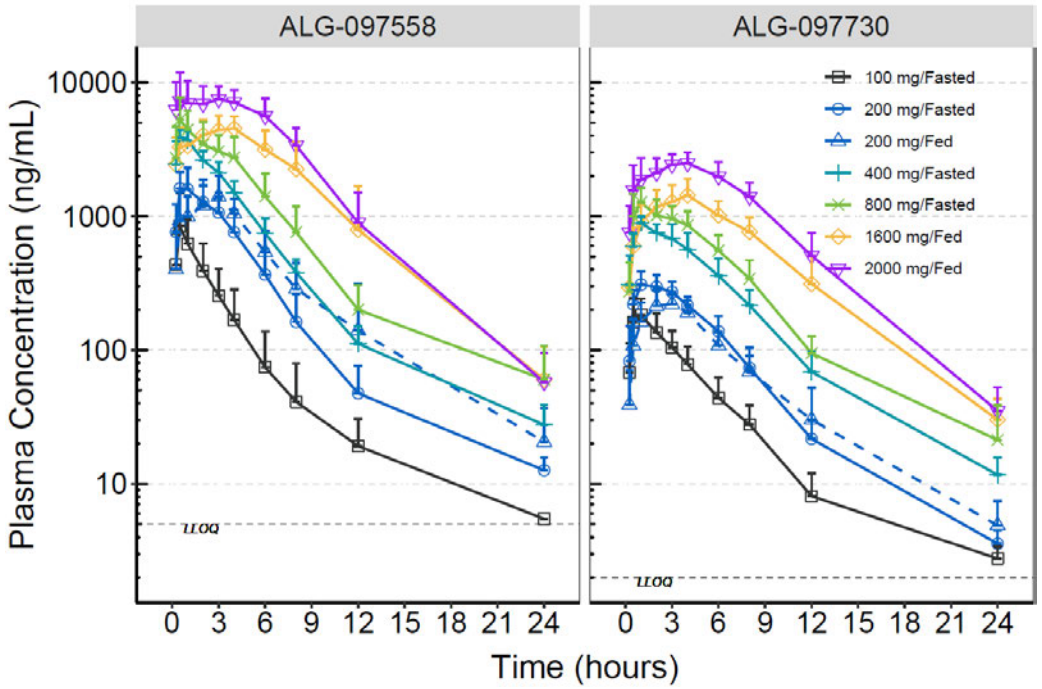


Table 2. Geometric Mean (% Geometric CV) Plasma PK Parameters of ALG-097558 Following a Single Oral ALG-097558 Dose in Healthy Volunteers in Study ALG-097558-701, Part 1

ALG-097558 Dose (mg)	No. of Subjects	C_{max} (ng/mL)	t_{max} (h)*	AUC_{0-12} (ng•h/mL)	AUC_{inf} (ng•h/mL)	C_{12h} (ng/mL)	CL_{ss}/F (L/h)	Vz/F (L)	$t_{1/2}$ (h)**
100 mg/ Fasted	6	753 (65.3)	0.5 (0.5,1)	1751 (63.5)	1779 (65.5)	5.68 (112)	63.2 (64.0)	155 (43.5)	2.00 (0.73)
200 mg/ Fasted	6	1679 (32.0)	0.75 (0.5,3)	6187 (41.5)	6437 (43.0)	40.1 (61.3)	31.1 (43.0)	127 (31.1)	2.99 (1.06)
200 mg/ Fed	6	1489 (38.5)	2.5 (0.5,4)	6993 (38.5)	7632 (43.6)	91.3 (125)	26.2 (43.6)	140 (37.6)	3.83 (1.07)
400 mg/ Fasted	6	4152 (13.1)	0.75 (0.5,1)	14359 (14.2)	15368 (14.7)	106 (36.1)	26.0 (14.7)	152 (36.0)	4.32 (1.69)
800 mg/ Fasted	6	5137 (39.7)	0.5 (0.5,3)	19985 (45.2)	21880 (48.8)	175 (53.5)	36.6 (48.8)	348 (34.7)	7.31 (3.80)
1600 mg/ Fed	6	4605 (19.2)	3.5 (2,8)	32488 (26.8)	36071 (31.2)	485 (112)	44.4 (31.2)	240 (25.0)	3.96 (1.41)
2000 mg/ Fed	9	8970 (34.4)	2 (0.25,6)	54721 (24.3)	58521 (25.7)	772 (68.8)	34.2 (25.7)	163 (36.7)	3.47 (1.17)

AUC_{0-24}=area under the concentration–time curve from 0 to 24 hours; AUC_{0-inf}=area under the concentration–time curve from 0 to infinity; C_{max}=maximum concentration; C_{24}=concentration at 24hr postdose; t_{max}=time to reach maximum concentration; $t_{1/2}$=plasma terminal half-life; CLss/F=apparent clearance; Vz/F=apparent volume of distribution.
*Median (minimum, maximum).
**Arithmetic Mean (SD).

Table 3. Preliminary Geometric Mean (% Geometric CV) Preliminary Plasma PK Parameters of ALG-097558 Following Multiple Oral ALG-097558 Doses in Healthy Subjects in Study ALG-097558-701, Parts 2 and 3

ALG-097558 Formulation/ Dose Q12H (mg)	No. of Subjects	Dose No.	C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-12} (ng·h/mL)	$t_{1/2}$ (h)**
Solution/350	6	1st Dose (Day 1)	3310 (30)	1 (0.25,1)	11000 (41.6)	ND
	6	14th Dose (Day 7)	3050 (26)	0.5 (0.25,1)	10100 (50.2)	6.13 (2.1)
Solution/800	5	1st Dose (Day 1)	5780 (37.5)	1 (0.5,2)	26400 (38.2)	ND
	5	14th Dose (Day 7)	3310 (51.4)	1 (0.5,1)	13100 (37.4)	4.01 (2.0)
Tablet/600	12	1st Dose	4770 (33.1)	4 (2,6)	24800 (32.2)	1.99 (0.33)
	12	9th Dose	4110 (25)	2.5 (1,4)	19100 (28.1)	2.06 (0.32)

AUC_{0-12}=area under the concentration–time curve from 0 to 12 hours; C_{max}=maximum concentration; ND=not determined; t_{max}=time to reach maximum concentration; $t_{1/2}$=plasma terminal half-life.
*Median (minimum, maximum).
**Arithmetic Mean (SD).

The details of Study ALG-097558-701 PK data are provided in Investigator's Brochure.

2.2.2.3 Conclusion

Based on available data, single oral doses of up to 2000 mg of ALG-097558 and multiple Q12H doses of up to 800 mg given for 7 days were well tolerated with acceptable PK properties in healthy volunteers. In conclusion, the favorable safety and PK data observed after dosing with ALG-097558 for ≤7 days in healthy volunteers support the continued clinical development of ALG-097558 and the evaluation of the impact hepatic impairment may have on the pharmacokinetics of ALG-097558 in this study.

2.3 Risk Benefit Assessment

2.3.1 Overall Benefit/Risk Assessment

No benefit can be expected for healthy subjects or subjects with hepatic impairment who participate in Study ALG-097558-702.

[redacted]

In Study ALG-097558-701, ALG-097558 was well tolerated with no SAEs, dose limiting toxicities and no evidence of a dose-dependent relationship with any adverse event (AE). While there is a risk of increased plasma exposures in subjects with hepatic impairment, the 200 mg Q12H ALG-097558 dose evaluated in this study provides a wide safety margin [redacted][4]. Further, supratherapeutic single doses of 2000 mg solution (equivalent to a 1250 mg tablet dose)—6.25-fold above the dose tested here—were well tolerated in Study ALG-097558-701.

ALG-097558 will be administered to subjects under close medical supervision in a clinical pharmacology unit with extensive experience in conducting hepatic impairment studies. Additionally, a comprehensive panel of safety assessments, including solicitation of AEs, laboratory investigations (hematology, serum chemistry, coagulation and urinalysis), electrocardiogram (ECGs), vital signs, and physical examinations will be performed at regular intervals throughout the study. A Study Review Committee (SRC) will be established to provide additional safety oversight. Other safety measures include protocol specific safety management guidance such as stopping criteria at the subject/cohort/trial level. Additional eligibility criteria have been incorporated for Cohort 1 to exclude those at highest risk of the serious adverse reactions associated with impaired hepatic function.

As a result, the overall risk profile for subjects participating in this study is considered to be low, [redacted], 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.

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

3.0 STUDY DESIGN

3.1 Summary

This Phase 1 non-randomized, open-label, multiple-dose, parallel-group hepatic impairment study consists of 2 cohorts, conducted in 16 subjects total, 8 subjects with moderate hepatic impairment (Cohort 1) and 8 subjects without hepatic impairment (Cohort 2), matched for age, body weight and, to the extent possible, for gender. The effect of hepatic impairment on the plasma pharmacokinetics of ALG-097558 will be assessed in subjects who have received multiple, twice daily (Q12H) oral (PO) doses of ALG-097558.

3.2 Hepatic Impairment Study Cohorts

3.2.1 Cohort 1

In Cohort 1, 8 eligible subjects with moderate hepatic impairment (Child-Pugh Class B, score 7-9) will receive multiple, Q12H PO doses of 200 mg ALG-097558 for 6 days (Days 1-6) for a total of 11 doses. Subjects will be followed-up for 14 days after the administration of study drug. The planned study design is depicted in the study schema in Figure 2.

Administration of ALG-097558 will be as a tablet in the fasted state. Refer to Section 6.3 for details on dose regimen administration with regard to food.

Reasonable efforts will be made to enroll an adequate number of subjects with Child-Pugh scores of 8 and 9 (1 to 3 subjects each) to ensure that the entire range of moderate hepatic impairment is represented.

3.2.2 Cohort 2

In Cohort 2, 8 eligible subjects without hepatic impairment will receive multiple, Q12H PO doses of 200 mg ALG-097558 for 6 days (Days 1-6) for a total of 11 doses. Subjects will be followed-up for 14 days after the administration of study drug. The planned study design is depicted in the study schema in Figure 2.

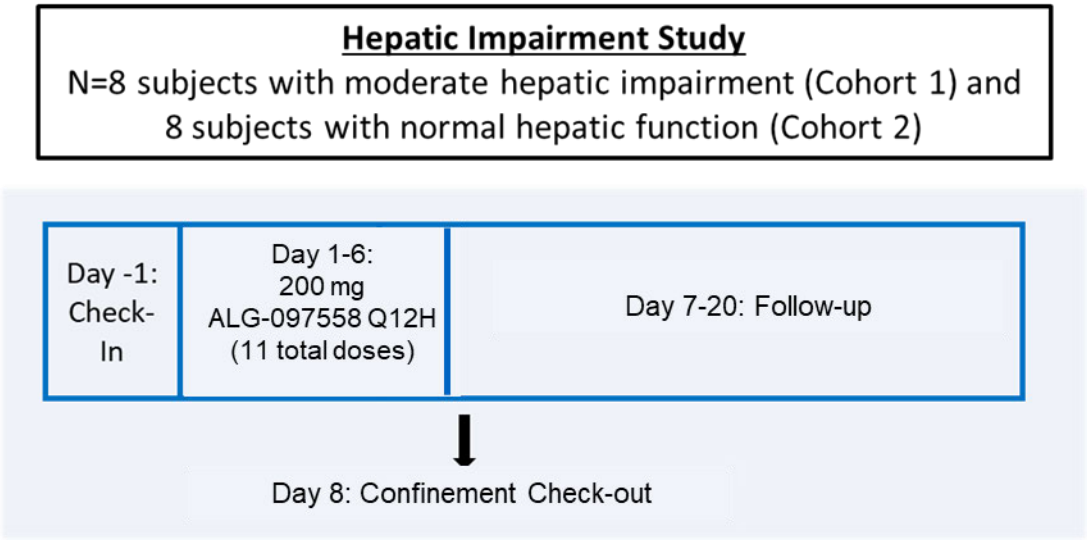
Administration of ALG-097558 will be as a tablet in the fasted state. Refer to Section 6.3 for details on dose regimen administration with regard to food.

Enrollment in Cohort 2 will not take place until all subjects in Cohort 1 complete the inpatient portion of the study. This staggered enrollment will help facilitate matching of the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; and, as much as practically possible, gender) between Cohorts 1 and 2.

3.3 Study Schema

The study schema is depicted in Figure 2.

Figure 2. Study Schema



See Section 7.0 for details of Study Procedures.

3.4 General Rules

Up to 3 additional subjects may be enrolled in Cohorts 1 and 2 at the discretion of the SRC and under the following conditions:

1) A subject(s) in the same cohort discontinues study drug prematurely for reasons other than a safety concern.
2) A cohort is considered to have insufficient data to enable evaluation, due to reasons including but not limited to:
   a) Emerging PK data show high inter-subject variability and the number of subjects is deemed inadequate for evaluation of the effect of hepatic impairment on ALG-097558 exposure.
   b) Missing data due to subject(s) lost to follow up.

3.5 Study Review Committee

In this study, an SRC will provide safety oversight for Cohorts 1 and 2, which includes conducting Data Review Meetings (DRMs), providing guidance on ongoing study management, reviewing emerging data (e.g., Cohort 1 safety and PK data), and providing recommendations to Aligos Therapeutics regarding actions the Committee deems necessary for the continued protection of subjects enrolled in the study. Examples of recommendation the SRC might make include:

1) Changing or adding a PK time point to better capture a specific PK criterion (e.g., T_{max});
2) Changing or adding a safety assessment time point to better capture safety information (e.g., changing ECG time point to better capture T_{max});
3) Enrolling additional subjects, if deemed necessary, as per General Rules (Section 3.4).
4) Modifying the dose based on emerging PK data.

The SRC is charged with formulating its recommendations in compliance with this protocol, in consideration of relevant external information and emerging data, and in a manner that strives to maintain an acceptable risk profile for study participants. Details of the SRC may be found in the SRC Charter.

The SRC will consist of the following individuals:

- 1 Principal Investigator
- Sponsor representatives (including the Medical Monitor)
- DMID Medical Monitor or Medical Officer

3.6 Data Review Meetings

The purpose of a DRM is to facilitate proper safety oversight by the SRC. Available preliminary cumulative safety and PK data (and any other data deemed necessary for proper evaluation) will be reviewed.

A planned DRM will be conducted after at least 6 days of preliminary safety and PK data are available for 2 subjects in Cohort 1 to confirm or modify the ALG-097558 dose for the remaining Cohort 1 subjects and subsequent Cohort 2 subjects. Unless otherwise instructed by the SRC, DRMs will then take place after 5 subjects and 7 subjects in Cohort 1 have completed dosing for6 days (11 doses total), respectively. Unless emerging data indicate otherwise, DRMs need not be conducted during dosing of Cohort 2.

Ad hoc DRMs may be requested by the SRC or Sponsor at any time for any reason.

3.7 Rationale for the Study and Study Design

This is a Phase 1 study conducted in subjects with and without hepatic impairment exploring the effect of hepatic impairment on the plasma pharmacokinetics of ALG-097558. SARS-CoV-2-infected patients with chronic liver disease are at risk for severe illness and represent a subpopulation that would be important to treat with direct acting antivirals like ALG-097558 which do not require coadministration with ritonavir. The current standard of care is Paxlovid, which contains ritonavir and is contraindicated in this subpopulation. Further, CYP3A4 is expected to be the predominant clearance mechanism for ALG-097558, and FDA guidance (FDA 2003) recommends a PK study in hepatically impaired subjects if hepatic metabolism accounts for a substantial portion of the elimination of a drug. Hepatically impaired subjects may have different exposure levels of ALG-097558 as compared with subjects without hepatic impairment due to altered metabolism in the liver. Consequently, it is important to evaluate what impact hepatic impairment may have on the pharmacokinetics of ALG-097558 for use in hepatically impaired patients. Findings from this study will be used to develop dosing recommendations so that dose and/or dosing interval may be adjusted appropriately in the presence of hepatic disease.

3.7.1 ALG-097558 Dose

The safety, PK, and bioavailability data from Study ALG-097558-701 support the 200 mg Q12H ALG-097558 dose (tablets) for evaluating the pharmacokinetics in hepatically impaired subjects. This dose was found to be safe in Study ALG-097558-701, where single doses of up to 2000 mg solution (equivalent to a 1250 mg tablet dose) and twice daily (Q12H) doses of up to 800 mg ALG-097558 solution for 7 days were well tolerated. Here, 200 mg Q12H ALG-097558 doses will be administered for 6 days for a total of 11 doses. In addition to having already established this as a well-tolerated dose in healthy volunteers, the 200 mg ALG-097558 Q12H dose was selected for this study because it is in the projected therapeutic range to be evaluated in Phase 2, while also being 19- to 26-fold below the NOAEL and 5-7-fold below the highest tested dose of 2000 mg in Study ALG-097558-701 based on exposure multiples calculated from $AUC_{0\text{-}24}$ and C_{max}. As an increase in plasma concentrations of ALG-097558 may be observed in subjects with hepatic impairment, this dose provides an adequate safety margin while still evaluating doses in the projected efficacious range in SARS-CoV-2-infected patients.

3.7.2 Dose Duration

This is a typical hepatic impairment reduced study design (FDA 2003), with Q12H doses for 6 days of ALG-097558 for a total of 11 doses administered. Because ALG-097558 and its active metabolite, ALG-097730 exhibit time-independent but non-linear (less than dose proportional) pharmacokinetics in the Phase 1 Study ALG-097558-701, a multiple dose design is appropriate to evaluate the impact of hepatic impairment on ALG-097558 disposition. The 11 total doses are sufficient to achieve steady state and define any potential time-dependent clearance in hepatically impaired subjects. Based on the preliminary PK data in Study ALG-097558-701, no plasma accumulation was observed. In addition, a 5-day dosing duration is the intended

therapeutic regimen in SARS-CoV-2-infected patients, and is supported by favorable safety data in Study ALG-097558-701 where 7 days of ≤800 mg ALG-097558 Q12H dosing was well tolerated.

3.7.3 Patient Populations

The choice of using subjects with moderate hepatic impairment (Cohort 1) and without hepatic impairment (Cohort 2) is standard in hepatic impairment studies with a reduced study design establishing the preliminary PK profile of a drug (FDA 2003). The Child-Pugh scale will be used to categorize the degree of hepatic impairment in Cohort 1 subjects, where only Child-Pugh Class B (score: 7-9) subjects will be enrolled. Reasonable efforts will be made to enroll an adequate number of subjects with Child-Pugh scores of 8 and 9 (1 to 3 subjects each) to ensure that the entire range of moderate hepatic impairment is represented. Subjects with severe hepatic impairment (Child-Pugh Class C, score: >9) will not be included because the percentage of subjects with severe hepatic disease is low; PK modeling analyses, including population PK, physiologically based PK modeling, and exposure–response analysis from later phase studies will be performed to inform ALG-097558 pharmacokinetics, safety, and efficacy in subjects with mild and severe hepatic impairment. The primary purpose of this study is to determine, based on the behavior of ALG-097558 in subjects with normal hepatic function, whether the pharmacokinetics and/or pharmacodynamics of ALG-097558 are altered in subjects with hepatic impairment to the extent that a dose adjustment would be indicated. For this reason, subjects in Cohort 2 will be representative of the intended patient population (with apparently normal hepatic function) and to the extent possible, should be similar to Cohort 1 subjects with respect to age, weight, and gender.

3.7.4 Open Label

Study ALG-097558-702 will be evaluating less intensive dosing regimens than those whose safety profile was defined in Study ALG-097558-701. This study therefore may be conducted in an open-label manner and is intended to build upon the safety database by evaluating the clinical profile of ALG-097558 in hepatically impaired subjects. Further, because the primary analysis is pharmacokinetics, a placebo control is not considered necessary.

3.7.5 Study Adaptability

A number of features have been incorporated into this protocol to allow for adaptations based on emerging information during the conduct of the study. Although adjustments are permitted for several study parameters, measures are established for each parameter to ensure such adjustments do not put subject safety at additional risk. The rationale for these built-in adaptations is provided in the following sections.

3.7.5.1 Visit Types

While certain visits are required to be of a stricter type (e.g., inpatient/confined), other study days/visits can be more flexible (e.g., outpatient, home visit). The nature of some study

assessments does not require a specific visit type for study data to be collected. Allowing different visit types permits COVID-19-related (or similar) accommodations needed at the time of study conduct that may otherwise prevent a planned safety/study visit from being performed.

3.7.5.2 Number of Subjects in a Cohort

The plan is to evaluate 8 subjects in both Cohort 1 and Cohort 2. The planned number of subjects are considered “standard” (i.e., sizes typically evaluated in hepatic impairment studies with a reduced study design). The number of enrolled subjects would only be modified if emerging data indicate larger cohort sizes are needed for an adequate assessment of pharmacokinetics. The protocol caps how much larger (+3 patients) each cohort may change in size.

3.8 End of Study Definition

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

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the comparative plasma pharmacokinetics of ALG-097558 and the metabolite ALG-097730, following multiple doses in subjects with moderate hepatic impairment and matched healthy subjects with normal hepatic function.

4.1.2 Secondary Objective

The secondary objective is:

- To evaluate the safety and tolerability of multiple oral doses of ALG-097558 in subjects with hepatic impairment and in matched healthy subjects with normal hepatic function

4.1.3 Exploratory Objectives

The exploratory objectives are:

- To evaluate the relationship between PK and safety
- To evaluate the relationship between continuous measures of hepatic impairment, such as bilirubin, ALT, AST, prothrombin time and serum albumin, and PK

4.2 Study Endpoints

4.2.1 Primary Endpoints

The primary endpoints of this study are:

- PK parameters of total and unbound ALG-097558 and the metabolite ALG-097730 in plasma, including but not limited to $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$, following multiple oral doses in subjects with moderate hepatic impairment (Cohort 1) and in subjects without hepatic impairment (Cohort 2)

4.2.2 Secondary Endpoints

The secondary endpoints of this study are:

- Safety data, including treatment-emergent AEs (TEAEs), physical examinations, vital signs, 12 lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology, liver function tests, and urinalysis)

4.2.3 Exploratory Endpoints

The exploratory endpoints may include, but are not limited to, the following:

- Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730, and safety data
- Evaluate emergent safety, which may include AEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory results with PK
- Evaluate liver function tests, including bilirubin, ALT, AST, prothrombin time and serum albumin, with PK
- Change from baseline at various timepoints for various liver function tests, including bilirubin, ALT, AST, prothrombin time and serum albumin

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Study Population

Cohorts 1 and 2 will consist of 8 subjects with moderate hepatic impairment and 8 subjects without hepatic impairment, respectively; male and female (18-75 years of age, inclusive).

5.2 Inclusion Criteria

5.2.1 Inclusion Criteria for All Subjects

1) Male or female between 18 and 75 years of age, inclusive, at the Screening visit
2) Female subjects must either be not of childbearing potential, as defined below, OR, if they are a woman of childbearing potential (WOCBP), they are only eligible if they and any non-sterile, male sexual partners agree to use highly effective contraceptive therapy as defined in Section 7.2.3.

   Woman not of childbearing potential defined as:

   a) Postmenopausal:

      A postmenopausal state is defined as no menses for at least 12 months without an alternative medical explanation. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.

      OR

   b) Permanently sterile:

      Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
3) Male subjects must agree to wear a condom during sexual intercourse and their female sexual partners must agree to use highly effective means of contraception. These contraceptive measures must be implemented, at a minimum, from the start of dosing until at least 90 days after the last dose.

   NOTE: *Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.*
4) Body mass index (BMI) of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lb).
5) Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6) Subjects who are willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

5.2.2 Inclusion Criteria for Subjects with Normal Hepatic Function (Cohort 2, only)

7) Good general health as defined by no clinically relevant abnormalities identified by:
   a) Medical history
   b) Vital signs in the following reference range:
      i) Systolic blood pressure: ≥90 to ≤150 mmHg
      ii) Diastolic blood pressure: ≥40 to ≤90 mmHg
      iii) Pulse rate: ≥40 to ≤100 beats per minute
8) Subjects must have a 12-lead electrocardiogram (ECG) that meets the following criteria:
   a) Heart rate between 40 and 100 beats per minute [bpm], extremes included;
   b) QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF) ≤450 ms (males) or ≤470 ms (females);
   c) QRS interval <120 ms;
   d) PR interval ≤220 ms;
   e) 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. Subjects with a retest (single) ECG without clinically significant abnormalities as per this inclusion criterion may be included.*

9) Subjects must fit the demographic-matching criteria, including:
   a) A body weight that is ±15 kg of the median of Cohort 1, as provided by the Sponsor;
   b) An age that is ±10 years of the median of the Cohort 1, as provided by the Sponsor;
   c) Attempts will be made to ensure that the male-to-female distribution in Cohort 2 is comparable to that in the hepatic impairment Cohort 1
10) Normal hepatic function with no known or suspected hepatic impairment.

5.2.3 Inclusion Criteria for Subjects with Impaired Hepatic Function (Cohort 1, only)

11) Absence of clinically significant abnormal screening medical history, physical examination, and clinical laboratory findings in the opinion of the Investigator; abnormal findings that are related to the subject's hepatic impairment and/or underlying condition which has resulted in their hepatic impairment are acceptable.
12) Subjects must have vital signs that meets the following criteria:
   a) Systolic blood pressure: ≥90 to ≤160 mmHg
   b) Diastolic blood pressure: ≥40 to ≤100 mmHg

c) Pulse rate: ≥40 to ≤100 beats per minute

13) Subjects must have a 12-lead electrocardiogram (ECG) that meets the following criteria:

a) Heart rate between 40 and 100 beats per minute [bpm], extremes included;

b) QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF) ≤470 ms (males and females);

c) QRS interval <120 ms;

d) PR interval ≤220 ms;

e) 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. Subjects with a retest (single) ECG without clinically significant abnormalities as per this inclusion criterion may be included.*

14) Subject satisfies the criteria for Class B of the Child-Pugh classification (Child Pugh Scores 7-9 points) within 28 days of study drug administration.

15) A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, FibroScan, computerized tomography scan, or magnetic resonance imaging (MRI).

16) Stable hepatic impairment, defined as no clinically significant change in disease status within 3 months prior to the Screening visit, as documented by the subject's recent medical history (e.g., no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or PT by more than 50%). If subjects do not have such records, 2 screening visits (at least 14 days apart) will be performed to demonstrate stability of the disease.

17) Stable concomitant medications (as defined in Section 6.9) for the management of an individual subject's medical history for at least 28 days. On a case-by-case basis, with input from the Sponsor, subjects receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

5.3 Exclusion Criteria

5.3.1 Exclusion Criteria for All Subjects

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1) Subjects with any current or previous illness that, in the opinion of the Investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject or 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, endocrine, neurologic, dermatologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances.
2) Subjects with a past history or risk factors for *Torsade de Pointes* syndrome (e.g., family history of long QT Syndrome) or recent (within past 6 months) history or clinical evidence at screening of clinically significant or unstable cardiac disease such as: angina, congestive heart failure, myocardial infarction, diastolic dysfunction, arrhythmia, ECG abnormalities, moderate to severe valvular disease or uncontrolled hypertension.
3) Subjects 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) Subjects with a recent (within 1 year of randomization) history or current evidence of use of amphetamines, barbiturates, narcotic or other drugs of abuse/recreational drug use. Use of these drugs under physician supervision (e.g., prescription narcotics for known pain disorder) and cannabis use are not exclusionary.
5) Excessive use of alcohol defined as regular consumption of ≥14 standard drinks/week for women and ≥21 standard drinks/week for men (Chalasani et.al. 2018). For current definition of a standard drink, please refer to the National Institute on Alcohol Abuse and Alcoholism website (https://www.niaaa.nih.gov/what-standard-drink).
6) Unwilling to abstain from alcohol use for 48 hours prior to start of study through end of study follow up.
    a) Positive urine alcohol test at screening or Day -1
    b) Positive pregnancy test at screening or Day-1
7) Subjects with current:
    a) Hepatitis B infection, defined as presence of HBsAg or HBV core antibody, unless, for Cohort 1, a subject meets the following criteria:
        i) On a stable HBV treatment regimen defined as currently receiving HBV nucleos(t)ide analogy (NA) therapy for ≥6 months prior to screening and have been on the same treatment regimen for ≥3 months at the time of screening; AND
        ii) Screening HBV DNA level <20 IU/mL; AND

iii) NA treatment regimen with no suspected/known risk of drug-drug interactions with ALG-097558

b) HAV infection (confirmed by hepatitis A antibody immunoglobulin M [IgM]).

c) Hepatitis C virus (HCV) infection (confirmed by HCV antibody and/or HCV RNA). Subjects who have been treated and achieved sustained virologic response ≥6 months prior to screening with HCV RNA <LLOQ, target not detected, remain eligible.

d) Anti-HEV IgM-positive and/or detectable HEV RNA level (only applies to subjects with history of living or traveling to an HEV epidemic area within 90 days of screening).

e) Human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection (confirmed by antibodies) at screening unless, for Cohort 1, a subject meets the following criteria:

i) On a stable HIV treatment regimen defined as currently receiving combination antiretroviral therapy (ART) for ≥6 months prior to screening and have been on the same treatment regimen for ≥3 months at the time of screening; AND

ii) Screening HIV-1 RNA level <LLOQ; AND

iii) CD4+ T cell count ≥350 cells/ml at screening and at least once during 12 months prior to screening; AND

iv) No history of AIDS-defining illness; AND

v) Combination ART regimen with no suspected/known risk of drug-drug interactions with ALG-097558

f) Acute infection, including SARS-CoV-2, at the time of randomization. If an acute infection is considered resolved prior to randomization, the subject remains eligible.

8) Subjects having received an unapproved investigational agent or vaccine within 4 weeks (or 5 half-lives, whichever is longer) prior to randomization

9) Use of prohibited medications (as described in Section 6.9) within 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study drug.

10) Subjects currently participating in another clinical or medical interventional research study.

11) Subjects who had major surgery (e.g., requiring general anesthesia) within 12 weeks before screening, or will not have fully recovered from surgery, or have surgery planned during the time the subject is expected to participate in the study, or within 4 weeks after the last dose of study drug.

NOTE: *Subjects with planned surgical procedures to be conducted under local anesthesia may participate.*

5.3.2 Exclusion Criteria for Subjects with Normal Hepatic Function (Cohort 2, only)

12) Estimated creatinine clearance <60 mL/min/1.73 m^2 at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula] – Unless otherwise instructed by the SRC, CKD-EPI should not be corrected for subjects of African ancestry

13) The following laboratory values are exclusionary:

a) Bilirubin (total, direct) >1.2× upper limit of normal (ULN) (unless Gilbert's is suspected), or

b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >1.2×ULN

c) Grade ≥1 Hemoglobin

5.3.3 Exclusion Criteria for Subjects with Impaired Hepatic Function (Cohort 1, only)

14) Subjects with advanced ascites (Grade 3)

15) Subjects with refractory encephalopathy as judged by the investigator.

16) Subjects with esophageal variceal bleeding within the past 6 months prior to screening.

17) Subjects with Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.

18) Estimated creatinine clearance <60 mL/min/1.73 m^2 at screening, calculated by the CKD-EPI formula] – Unless otherwise instructed by the SRC, CKD-EPI should not be corrected for subjects of African ancestry

19) The following laboratory values are exclusionary:

a) ALT or AST level ≥5×ULN, or

b) Serum sodium ≤125 mmol/L, or

c) Platelets <50×10^9/L

d) Grade ≥2 Hemoglobin

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. Subjects with a retest value that is no longer exclusionary may be included.

a. Vital signs can be repeated in the same or subsequent visit
b. Laboratory tests should be repeated anytime within the screening window

5.4 Subject Screening and Enrollment

Screening procedures will occur only after a subject has signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Ethics Committee approved ICF and provides authorization to use protected health information. The ICF will be completed prior to any study specific procedures. The use of a site-specific generic prescreening protocol, approved by the local IRB/IEC, may be used prior to study screening at the Sponsor's discretion.

To enroll, the Investigator will verify eligibility according to all inclusion and exclusion criteria (Section 5.2 and Section 5.3). Any questions regarding eligibility should be addressed to the Sponsor's Medical Monitor prior to enrollment.

A screening examination should be performed between -28 and -2 days before the start of the study (Day 1). For Cohort 1 subjects, if stability of hepatic impairment needs to be demonstrated (Inclusion criterion 14), 2 screening visits (at least 14 days apart) will be performed.

A screen failure log must be maintained by the Investigator.

At the screening examination, the procedures outlined in Section 7.0 will be performed to establish each candidate's general health and qualifications for enrollment into the study.

For re-screened subjects who were previously screened and found to be eligible but were not enrolled due to limited enrollment availability or other nonmedical reasons, the screening procedures outlined in Section 7.0 should be repeated with the exclusion of the following:

- Biochemistry and hematology if taken within the past 30 days
- HIV-1, HIV-2, Hepatitis A, B, C and E (if applicable)

5.5 Subject Completion

A subject will be considered to have completed the study if Day 20 assessments have been completed.

5.6 Study Duration

Subjects will be followed for 14 days following administration of the last dose of the study drug. The study duration for each subject, not inclusive of the 28-day screening window, will be ~3 weeks.

5.7 Cohort Enrollment Guidelines

5.7.1 Cohort 1 Enrollment Guidelines

Enrollment of subjects with moderate hepatic impairment (Cohort 1) will initiate first. The Child-Pugh classification system (Table 4; Table 5) will be used to define the cohort of subjects

with moderate hepatic impairment (Child-Pugh Class B). Reasonable efforts will be made to enroll an adequate number of subjects with Child-Pugh scores of 8 and 9 (1 to 3 subjects each) to ensure that the entire range of moderate hepatic impairment is represented.

Table 4. Study Cohorts Based on Hepatic Function

Cohort	Description	Child-Pugh Score	No. of Subjects [a]
1	Moderate hepatic impairment	Class B (7 to 9 points)	8
2	Normal hepatic function	Not Applicable	8

[a] Up to 3 additional subjects per cohort may be enrolled at the discretion of the SRC (see Section 3.4).

Table 5. Assessment of Hepatic Impairment: Child-Pugh Scale

Assessment Parameters	Assigned Score for Observed Findings		
	1 point	2 point	3 point
Encephalopathy grade	0	1 or 2 (or suppressed with medication)	3 or 4
Ascites	Absent	Slight	Moderate
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, seconds prolonged	<4	4 to 6	>6

5.7.2 Cohort 2 Enrollment Guidelines

Subjects with normal hepatic function (Cohort 2) will only be enrolled after all subjects in Cohort 1 complete the inpatient portion of the study. This staggered enrollment will help facilitate matching of the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; and as much as practically possible gender) between Cohorts 1 and 2.

5.8 Stopping and Discontinuation Criteria

5.8.1 Subject Stopping Criteria

The primary consideration in any determination to discontinue a subject's participation must be the health and welfare of the subject. A subject will be discontinued from study drug whenever the Investigator believes that, for safety reasons (e.g., AE), it is in the best interest of the subject to discontinue study drug treatment. In such cases, the Investigator is encouraged to contact the Aligos Medical Monitor before discontinuing the subject from the study, if the subject's medical condition allows for it. Additionally, any subject meeting one or more of the following criteria will be automatically discontinued from study drug are:

- Pregnancy

- The subject has a SAE or Grade ≥3 TEAE (*with the exception of QTcF prolongations, for which specific criteria are provided below*) that is attributed (i.e., related, see Section 8.2.3) to study drug
- Confirmed QTcF of >500 ms ***OR*** ≥60 ms above baseline

  Notes:
  - 2 additional ECGs will be collected approximately 2-4 minutes apart to confirm the original measurement.
  - For hepatic impairment subjects in Cohort 1, a confirmed QTcF interval that is increased by ≥30 ms from baseline **and** >470 ms may also result in study drug discontinuation (see Section 7.2.2.2).
- Increases in ALT as defined in Section 8.5.1, including severe worsening of hepatic disease (Cohort 1 subjects only)
- A subject requires prolonged treatment with any of the disallowed medications listed in Appendix B (Prohibited Medications), and it is considered contraindicated to be dosed concurrently with study drug
- An event occurs that triggers the study treatment stopping criteria for the cohort or the whole study (Section 5.8.2 and Section 5.8.3)

5.8.2 Cohort Stopping Criteria

For Cohorts 1 and 2, further dosing and enrollment will be stopped if any of the following criteria are met and confirmed:

- Occurrence of ≥1 SAE that is attributed (i.e., related, see Section 8.2.3) to study drug, OR
- ≥2 subjects experience TEAEs that result in premature discontinuation of study drug and are attributed (i.e., related, see Section 8.2.3) to study drug, OR
- ≥2 subjects experience Grade ≥3 TEAEs of a similar nature (defined by MedDRA preferred terms) that are attributed (i.e., related, see Section 8.2.3) to study drug

Criteria will be applied separately to each cohort.

5.8.3 Study Stopping Criteria

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Safety signals from this or other studies indicate a potential health hazard to subjects as described in Section 5.8.1 Subject Stopping Criteria and Section 5.8.2 Cohort Stopping Criteria.
- A decision from the IRB/IEC, or regulatory authority to terminate the study.

5.8.4 Subject Discontinuation Criteria

A subject may be discontinued from study drug for non-safety-related reasons. In such cases, the Investigator is encouraged to contact the Aligos Medical Monitor before discontinuing the subject from the study. Additionally, any subject meeting the following criteria will be discontinued from study drug:

- Significant noncompliance with study drug
- Significant noncompliance with study schedule
- Study Terminated by Sponsor (Section 5.8.5)

5.8.5 Study/Site Discontinuation Criteria

The Sponsor has the right to terminate this study or remove a participating investigational site at any time for non-safety-related reasons (i.e., operational), which may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.
- Sponsor's decision to terminate the study at any time for any reason.

5.8.6 Procedures for Subjects Who Discontinue Treatment

Subjects are free to discontinue their participation at any time during this clinical trial. Additionally, the Investigator has the right to remove any subject from study drug administration or participation in the study. However, Aligos requests that, where feasible, the Investigator consults with the Sponsor's Medical Monitor before discontinuing study medication permanently. **For any subject who prematurely discontinues study treatment before the end of the treatment phase, all attempts should be made to complete all scheduled follow-up evaluations to ensure maximal safety oversight.**

Subjects who discontinue study medication should undergo the Study Completion procedures tabulated in Section 7.1 for the purpose of safety monitoring within 72 hours after their last dose of study medication. Any subject who discontinues with ongoing AEs should be followed until resolution of their AE(s) or until the Investigator has determined that the AE(s) has stabilized. In addition, subjects should be followed up per the Schedule of Events tables (Section 7.1) to the final follow-up visit.

5.8.7 Documentation of Discontinuation of Subjects

The reasons for early discontinuation of any subject must be documented on the appropriate case report form (CRF). If the reason for early discontinuation is an AE or an abnormal laboratory value, record the specific event or test result on the AE CRF, and monitor the subject until the event is resolved or deemed stable by the Investigator.

5.8.8 Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject is lost to follow up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the electronic case report form (eCRF) and in the source document. Study drug assigned to the withdrawn subject will not be assigned to another subject. Subjects who withdraw for non-safety reasons may be replaced (see Section 5.8.9). Subjects who withdraw consent during the treatment or follow-up phase will be requested to complete an optional safety follow-up visit, at which the assessments from the study visit as designated in the Schedule of Events table should be performed.

Subjects who discontinue may withdraw consent for use of their samples for future research (see Section 12.7). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

5.8.9 Replacement of Subjects

If a subject withdraws from the study for non-safety reasons, replacement of the subject may be considered as per the general rules (Section 3.4).

6.0 DOSING REGIMEN

6.1 ALG-097558 (All Cohorts)

Subjects will be assigned to receive multiple PO doses of 200 mg ALG-097558 Q12H starting the morning of Day 1for 6 days for a total of 11 doses. ALG-097558 will be administered in the fasted state. For dosing in the fasted state, the ALG-097558 dose will be administered with ~240 mL of water at ambient temperature. Except as part of dosing, water may be consumed freely until 1 hour before dosing through 2 hours after dosing. Dietary requirements are as follows:

Days 1-6: Administration of ALG-097558 will be in the fasted state. Specifically, subjects will fast from food for at least 2 hours prior to dosing until at least 2 hours after for each dose of study drug.

6.2 Description of Study Drug

ALG-097558 will be supplied as 100 mg strength SDD tablets. To achieve the 200 mg ALG-097558 dose, subjects will receive 2×100 mg strength tablets. Additional information may be found in the Pharmacy Manual.

The manufacturer will provide a certificate of analysis and a batch release certificate for batches of investigational medicinal product used in the study.

6.3 Dose Preparation and Administration

Study medication will be dispensed by the licensed investigational pharmacist or other authorized personnel with appropriate training.

Additional information for dose preparation and administration can be found in the Pharmacy Manual.

6.4 Overdoses

A calculated dose that exceeds its correct dose by >50% and is administered to the subject will be considered an overdose and documented as an AE. In the event of an overdose the Investigator should contact the Sponsor Medical Monitor to discuss further management of the subject.

In the event that a subject is administered an accidental overdose of the planned dose and the subject is asymptomatic and deemed clinically stable, continued dosing may be permissible after discussion with the Sponsor Medical Monitor.

6.5 Dose Modifications

Study dose modifications (e.g., for safety, tolerability concerns) may be considered following a review by the SRC of emerging data, including after review of preliminary safety and PK data at a DRM (see Section 3.6). Individual subject dose modifications by the Investigator are not allowed.

6.6 Ordering Study Drug

To order study drug, refer to the Pharmacy Manual.

6.7 Drug Accountability

Study site personnel will maintain adequate records of the receipt and disposition of all study medication shipped to the site. Records must include dates, lot numbers, quantities received, quantities dispensed and the identification number of each subject who has received each lot of study drug.

The Investigator will not supply study drug to any person not authorized to receive it.

6.8 Disposition of Used, Partially Used, and Unused Study Medication Containers

All used and unused study drug supplied by Aligos must be retained by the pharmacist. Periodically throughout and at the conclusion (or suspension, termination, or discontinuation) of the study, a representative of Aligos or its designated agent will conduct inventories and accountability of study materials. If applicable, once accountability is completed, an Aligos representative or designee will authorize the return of all used and unused study medication containers to a designated facility. For study medication containers returned to Aligos or its designated agent, records will include dates, lot numbers, and quantities of study drug returned. Local destruction of study drug is permitted where appropriate methods of destruction are available.

6.9 Prior and Concomitant Medications

6.9.1 All Subjects

All medications (prescription and over-the-counter), vitamins and/or herbal supplements taken within 28 days of study screening and during the study, will be recorded in the CRF with indication, dose information and dates of administration.

Subjects on medications that are sensitive CYP3A4 substrates with narrow therapeutic index should be monitored carefully for loss of efficacy. These medications include, but are not limited to: alfentanil, astemizole, cisapride, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine.

Note: Sensitive CYP450 substrates refer to drugs whose plasma AUC values have been shown to increase 5-fold of higher when co-administered with known CYP inhibitors. For an updated list, see: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems

Use of the following medications are prohibited within 28 days (or 5 half-lives, whichever is longer) prior to the dose of study drug through the end of the study:

- Investigational products not specified in this protocol
- Sensitive substrates, inhibitors and/or inducers of CYP enzymes and/or transporters as identified by in vitro studies and the Phase 1 first-in-human study (Appendix B).
- Moderate inhibitors and/or inducers of CYP3A4 and/or P-gp (Appendix B)
- Herbal product(s) which has suspected/known risk of DDIs. Use of herbal products is strongly discouraged even in the absence of suspected DDIs.

Note: The list of prohibited medications is subject to change based on emerging information related to the study drugs (e.g., DDI study results) or other medications (e.g., new information from the medical literature).

Questions related to medications to treat AEs should be discussed with the Sponsor's Medical Monitor, whenever feasible, to minimize the risk of unintended DDIs.

The use of a prohibited medication may result in discontinuation of study drug, particularly if it is deemed to put a subject at unacceptable additional risk (e.g., due to enhanced risk of DDIs) or to confound the interpretation of the subject's data (e.g., pharmacokinetics or safety). Subjects who discontinue study drug due to use of a prohibited medication will be followed up as outlined in Section 5.8.6.

6.9.2 Subjects with Impaired Hepatic Function (Cohort 1)

Subjects are permitted to be on stable doses of background medications if they are considered necessary for the welfare of the study subjects (i.e., standard therapy for the underlying disease) and are not on the Prohibited Medications list (Appendix B). Whenever possible, attempts must be made to not alter the doses and regimens of the concomitant medications after Day 1 and until the end of Day 8.

Except for the aforementioned allowed concomitant treatments and the treatment of AEs if deemed medically necessary by the Investigator, the following restrictions apply:

- Nonsteroidal anti-inflammatory drugs are the preferred analgesics. Although acetaminophen/paracetamol use is not encouraged due to its known risk of hepatotoxicity, if its use is required, acetaminophen/paracetamol may be used at doses of ≤1 g/day.
- Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis after approval by the Sponsor.

6.9.3 Subjects with Normal Hepatic Function (Cohort 2)

In general, subjects will abstain from all concomitant treatments (prescription or nonprescription) except for the treatment of AEs if deemed medically necessary by the Investigator. Of note, the following restrictions apply:

- Nonsteroidal anti-inflammatory drugs are the preferred analgesics. Although acetaminophen/paracetamol use is not encouraged due to its known risk of hepatotoxicity, if its use is required, acetaminophen/paracetamol may be used at doses of ≤3 g/day.
- Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis after approval by the Sponsor.

6.10 Special Precautions

1. If a subject has had a recent febrile illness (with temperature >100.4F), the (first) administration of study drugs should be postponed until body [e.g., aural] temperature is normal for at least 72 hours.
2. Subjects must not donate blood during the study and for at least 90 days after the last dose of study drug.
3. Subjects may not use drugs such as amphetamines, benzodiazepines, cocaine, opioids, methadone, and barbiturates during screening and for the duration of the study, except under physician supervision (e.g., prescription narcotics for known pain disorder).
4. Subjects should not consume any food containing poppy seeds or codeine containing formulation starting 72 hours before screening and before admission to study site on Day -1 (to avoid false-positive drug screening test) until the last follow-up visit.
5. Subjects must not consume any food or drink/beverage containing alcohol from 1 week prior to start of study (Day -1) until the last follow-up visit.
6. Grapefruit, grapefruit juice, and Seville oranges will be requested not to be consumed within 14 days prior to administration of study drug (Day 1) and throughout the study until last dose.
7. Subjects will be requested to not consume apple or orange juice, citrus fruits, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats from 7 days prior to administration of study drug (Day 1) and throughout the study until the last dose.
8. Subjects will be requested to not consume any food or drink/beverage containing quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine) from 24 hours prior to administration of study drug (Day 1) and throughout the study until the last dose.
9. Subjects should be requested to refrain from any strenuous activities from 2 days before the screening visit through study follow up. Light ambulatory activities are permitted.

7.0 STUDY PROCEDURES

7.1 Schedule of Events

The schedule of study events and procedures is presented in Table 6. Procedures are summarized in Section 7.2.

Table 6. Schedule of Events

Assessment \ Day	SCR [a]	Check-in															
	-28 to -2	-1	Day 1 (hours relative to dosing)											2	3	4	5
			-1.25	-0.75	0 h	+0.25	+0.5	+1	+2	+3	+4	+6	+8	+12				
Obtain informed consent before any study procedures	X																	
Demographics	X																	
Medical/surgical history	X [a]	X (interim)																
HIV-1, HIV-2, Hep A, B, C & E tests [b,c,d]	X																	
CD4 count [e]	X																	
Drug and alcohol screen [f]	X	X																
FSH [g]	X																	
Pregnancy test [h]	X	X																
Confirm eligibility status [i]		X																
Outpatient visits	X																	
Confined to study site		X	X											X	X	X	X	
Enrollment [j]			X															
Study drug administration [k]					**X**									**X (PM dose)**	X	X	X	X
Physical examination [l]	X	X								X					X	X	X	X
12-lead ECG [b, m]	X	X	X				X	X	X		X				X	X	X	X
Vital signs [b,n]	X	X	X				X	X	X		X		X		X	X	X	X
Biochem, hematology & coagulation [b]	X	X		X												X		X
Urinalysis [o]	X	X														X		X
Plasma PK sampling [b, p]				X		X	X	X	X	X	X	X	X	X (predose PM dose)	X	X	X	X
Stored plasma sample [q]		X																
Adverse events	X																	
Concomitant medication	X																	

Table 6. Schedule of Events (cont'd)

Day	Day 6 (hours relative to dosing)													7	Check-out [r] 8	Follow-Up 20±1
Assessment	**–1.25**	**–0.75**	**0 h**	**+0.25**	**+0.5**	**+1**	**+2**	**+3**	**+4**	**+6**	**+8**	**+12**	**+14**			
Pregnancy test																X
Outpatient visits																X
Confined to study site	X													X	X	
Study drug administration [k]			**X**													
Physical examination [l]								X							X	X
12-lead ECG [b,m]	X				X	X	X		X						X	X
Vital signs [b,n]	X				X	X	X		X		X				X	X
Biochem, hematology & coagulation [b]															X	X
Urinalysis [o]															X	X
Plasma PK sampling [b,p]		X		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X															
Concomitant medication	X															

[a] For Cohort 1 subjects without records demonstrating stable hepatic disease within 3 months prior to screening (see Inclusion Criteria #14), 2 screening visits (at least 14 days apart) should be performed to demonstrate stability of the disease.
[b] 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.
[c] For the Hep B test, Cohort 1 subjects with history of stable chronic Hepatitis B infection (as defined in the eligibility criteria) only require HBV DNA testing. For the HIV tests, Cohort 1 subjects with history of stable HIV-1 infection (as defined in the eligibility criteria) only require HIV-1 RNA testing.
[d] Hepatitis E testing only required for subjects who have lived in or visited Hepatitis E endemic areas within 90 days of screening.
[e] Only applicable for Cohort 1 subjects with history of stable HIV-1 infection.
[f] Refer to the protocol for additional information on drug and alcohol screening.
[g] FSH at screening to confirm post-menopausal status in applicable subjects.
[h] Serum pregnancy test at screening, urine pregnancy test at all other visits.
[i] 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 assessments, the subject will not be randomized into the study.
[j] Enrollment can occur any time predose.
[k] Administration of ALG-097558 will take place at approximately the same time(s) each day Q12H. Dosing will occur in the fasted state, and subjects will fast for at least 2 hours before until at least 2 hours after dosing. Except as part of dosing, water may be consumed freely except between 1 hour prior to and 2 hours after dosing. A dosing window of ±1-hour within the nominal time will be allowed for administration of the study medication(s).

[l] A complete physical examination, including height (screening only) and body weight measurement, will be performed at screening and Day 20. A symptom-directed physical examination will be performed at any time as indicated at all other visits.
[m] For Cohort 1 and 2 subjects, single 12-lead ECGs will be collected during screening, at specified times on Day 1 and Day 6 as depicted in this Schedule of Events table, and at any time on Day 8 and the Follow Up Visit. For Cohort 1 subjects, single 12-lead ECGs will also be collected at Pre-AM dose (-1.25 hours) and at 4 hours ±30 minutes post-AM dose on Days 2, 3, 4, and 5 and for Cohort 2 subjects, single 12-lead ECGs will also be collected at any time on Day 3. Subjects must have been resting in the supine or semi-recumbent fashion for at least 10 minutes.
[n] Vital signs (body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate) will be measured in the supine or semi-recumbent position after resting for 5 minutes. Vital signs will be collected at Day 1 and Day 6 (predose, and at 0.5, 1, 2, 4, 8 hours postdose) or at any time for other visits depicted in the table.
[o] If urinalysis is positive, urine will need to be sent for microscopy, culture sensitivity (MCS).
[p] Blood samples for pharmacokinetics will be collected as specified:

Day / Collection	1	2	3	4	5	6	7	8
Pre-AM dose (hours)	X	X	X	X	X	X	-	-
Post-AM dose (hours)	X (0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 (pre-2nd dose))	-	-	-		X (0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 14)	-	-
Post-final dose (hours)	-	-	-	-	-		X (24, 36)	48

[q] Stored plasma samples may be used for PK assay validation.
[r] 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.

7.2 Assessment and Review of On-Study Evaluations and Procedures

This study systematically collects a broad panel of safety, and PK parameters throughout its conduct. The exact timing of collection of these parameters, which are defined below, is specified in the Schedule of Events table (Section 7.1).

Where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the following order of events should be adhered to, where possible:

- Obtain ECGs first and then vital signs, as close as possible to scheduled times but prior to blood specimen collections.
- Other than the PK collection times (see Section 7.2.1.1), assessments conducted within 20% of the nominal time (e.g., within 12 minutes of a 60-minute timepoint) from dosing will not be captured as a protocol deviation as long as the exact time of the assessment is noted on the source document and data collection record (e.g., eCRF).
- All other procedures should be obtained as close as possible (within 20% of the nominal time) to the scheduled time and may be obtained before or after blood specimen collection.

7.2.1 Pharmacokinetic Evaluations

7.2.1.1 Pharmacokinetic Blood Sampling

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

All efforts will be made to obtain PK samples at the exact nominal time relative to dosing. However, samples obtained within 15% of the nominal time (e.g., within 9 minutes of a 60-minute timepoint) from dosing will not be captured as a protocol deviation as long as the exact time of the sample collection is noted on the source document and data collection record (e.g., CRF). Predose samples must always be collected prior to dosing.

Blood samples will be collected to determine the concentration of ALG-097558 and the metabolite ALG-097730, if applicable, at times specified in the Schedule of Events (Table 6). Blood samples will be assessed for total concentrations of ALG-097558 and the metabolite ALG-097730 using validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) methods. Blood samples will be assessed for unbound concentrations of ALG-097558 and the metabolite ALG-097730, and quantified using a qualified equilibrium dialysis or ultra filtration followed by detection using a qualified LC-MS/MS method.

Details on the collection, processing, and storage of ALG-097558 PK samples are provided in the Pharmacokinetic Sample Processing Manual.

A stored plasma sample will be collected on Day -1 to enable PK unbound assay method development and validation per FDA guidelines for PK analysis of subjects with hepatic impairment.

PK samples may also be collected on an ad hoc basis as a safety assessment in the event that a safety event arises, for which an understanding of drug exposure is clinically important.

7.2.2 Safety Evaluations

The planned safety evaluations in this study include those which are "standard" in early phase studies as well as those which are specific to ALG-097558 based on the known clinical and nonclinical profile, and possible risks.

Adverse events, which will be captured throughout the study, are described in Section 8.0.

7.2.2.1 Laboratory Evaluations

Blood samples for a broad array of laboratory parameters (Appendix C) will be collected as detailed in the Schedule of Events and will be assessed at a designated laboratory.

Unless otherwise indicated, laboratory specimens should be collected predose and in the fasted state.

7.2.2.2 12-Lead Electrocardiograms

The Investigator will be responsible for evaluating the results and determining if any findings are of clinical significance. A description of the overall assessment (i.e., normal or abnormal including the reason) will be made within the CRF. Single ECGs will be obtained in a supine or semi-recumbent position at screening and all other timepoints specified in Table 6. The subject should be at rest and in a supine or semi-recumbent position for at least 10 minutes before ECG recordings and remain resting and in that position during the recording. ECGs may be repeated at the Investigator's discretion to account for erroneous readings.

All ECG recordings must be performed using a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements.

Cohort 1 Hepatic Impairment Subjects

For Cohort 1 subjects with hepatic impairment, additional monitoring will occur if a post-baseline QTcF interval is increased by ≥30 ms from baseline **and** >470 ms. Two additional ECGs will be collected approximately 2-4 minutes apart to confirm the original measurement. For a confirmatory QTcF value that meets subject stopping criteria (Section 5.8.1), study drug dosing will be discontinued. For other confirmatory QTcF values that remain above the threshold value but do not trigger the stopping criteria, a single ECG must be repeated at least hourly for up to 4 hours until QTcF values from 2 successive ECGs fall below the threshold value that

triggered the repeat measurement. Study drug dosing **cannot** continue occur until QTcF values from 2 successive ECGs fall below the threshold value. If, after 4 hours (or sooner, at the discretion of the Investigator), the QTcF values remain ≥30 ms from baseline **and** >470 ms for Cohort 1 subjects with hepatic impairment; or QTcF intervals get progressively longer, the subject will be discontinued from study drug dosing.

Subjects discontinued from study drug dosing due to QTcF values should undergo continuous ECG monitoring. Moreover, a cardiologist should be consulted if QTcF intervals do not resolve to less than the above criteria after 8 hours of monitoring (or sooner as per the judgment of the Investigator).

7.2.2.3 Vital Signs

Vital signs (body [e.g., aural] temperature, respiratory rate, automated blood pressure, and pulse rate) will be obtained in a supine or semi-recumbent position after ≥5 minutes of rest. Blood draws will take place after vital signs in the event that the 2 procedures need to be conducted at the same time. In this case, vital signs should be obtained as close to the scheduled time as possible, after ECG assessments and prior to blood collections.

7.2.2.4 Physical Examinations

A complete physical examination (including height at screening only and body weight measurement) will be performed as indicated in the Schedule of Events. A symptom-directed physical examination will be performed at any time at all other visits as indicated in the Schedule of Events (Table 6). BMI will be calculated by clinic staff at the screening visit using the following formula (rounded to one decimal place):

$$\text{BMI} = \text{weight in kg} \div (\text{height in meters})^2$$

7.2.3 Contraception

Contraception requirements from screening through completion of the study are defined in the Inclusion Criteria (Section 5.2). Additional information about contraception is provided below:

1. Male subjects must wear a condom during sexual intercourse from the start of dosing until at least 90 days after the last dose. Their nonsterile female partner must use a highly effective method of contraception (e.g., intrauterine device, hormonal contraceptives [see Appendix E]) throughout study drug administration and for at least 90 days after the last dose of study drug.

   NOTE: *A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.*

2. Female subjects who are of childbearing potential and sexually active with a non-sterile male partner must use a relevant highly effective method of contraception as listed in Appendix E. Their male partners must use effective methods of birth control such as a barrier method of contraception (e.g., condom with/without spermicidal foam/gel/film/cream/suppository) throughout study drug administration and for at least 90 days after the last dose of study drug.
3. A female subject must agree not to donate eggs (ova, oocytes) from screening onward until at least 90 days after the last dose of study drug.
4. A male subject must agree not to donate sperm during the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug.

7.2.4 Visit Types

Every effort will be made to maintain the visit types outlined in the Schedule of Events (Section 7.1). In the event of unforeseen circumstances such as pandemic-related hospital or clinic modifications or closures, visit types (i.e., confined, remote) may be modified. Subject safety will be the first priority when any modifications are considered or implemented. Assessments at a given visit may also be modified or omitted if necessary to maintain patient safety.

8.0 SAFETY MONITORING AND REPORTING OF ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An AE is any event, side effect, or untoward medical occurrence in a subject enrolled in a clinical trial whether or not it is considered to have a causal relationship to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the Investigator, physical examination finding, or disease temporally associated with participation in the study or use of the study drug, whether or not the event is considered related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

8.1.2 Pretreatment Adverse Events

A pretreatment AE is any event that meets the criteria for an AE/SAE and occurs after the subject signs the ICF but before receiving the first administration of study drug.

8.1.3 Treatment-Emergent Adverse Events

A TEAE is any event that meets the criteria for an AE/SAE and occurs on or after the time the subject received the first administration of study drug.

8.1.4 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death: This includes deaths that appear to be completely unrelated to study medication (e.g., a car accident).
- Is a life-threatening event: An event that places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires overnight inpatient hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect in the offspring of a study subject.
- Medically important event: An event that may not be immediately life-threatening, or result in death or hospitalization, or require intervention to prevent one of the outcomes listed above, but is considered medically significant for other reasons. For example, an opportunistic or otherwise unusual infection for the Investigator's practice, such as tuberculosis, will be considered medically significant.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

8.2 Documenting and Reporting of Adverse Events (including SAEs)

The Sponsor collects AEs from the period starting immediately after each subject signs the ICF. AEs will be evaluated and documented using the grading scales contained in Appendix F.

8.2.1 Documenting and Reporting Pretreatment Events

For enrolled subjects, record all pretreatment AEs that occur after the subject signs the ICF but before the first study drug administration on the AE CRF and Clinical Trials SAE Form (if applicable). The AE CRF and SAE form will indicate that the event occurred prior to the first dose of study drug.

8.2.2 Documenting and Reporting TEAEs

Record all AEs that occur from Day 1 (from start of study medication administration) to the last follow-up visit, regardless of the intensity, seriousness, or relationship to study drug, on the AE CRF, for all enrolled subjects. For subjects who do not enroll (i.e., screen failures), collect AEs until the time of screen failure.

Once an event has resolved, any recurrence will be reported as a new event with a corresponding grade. The intermittent nature of an AE should be taken into consideration when resolving an AE or reporting a new event. In addition, worsening in severity of a reported AE should be reported as a new AE with the corresponding grade.

Changes in objective findings (e.g., laboratory, ECG, physical examination) should be considered AEs only if they meet any of the following criteria:

- Associated with accompanying symptoms
- Require medical/surgical intervention
- Lead to discontinuation from the study
- Lead to significant additional concomitant drug treatment, or other therapy
- Considered clinically significant by the Investigator
- Lead to any of the outcomes included in the definition of an SAE

Whenever possible, the etiology of the abnormal findings (rather than the abnormal finding(s) itself) should be documented as the AE. For example, a subject with a presumed upper respiratory tract infection should be reported to have an AE of “upper respiratory tract infection” rather than having all of the following separate findings/AEs: “runny nose,” “cough,” malaise,” “fever”. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated. An AE includes the following:

- Pre-existing event that increases in frequency or intensity
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, prior to the first dose of study drug
- Laboratory abnormalities outside of normal limits and requiring therapeutic intervention

- An overdose of the study drug without any signs or symptoms will be considered an AE. A calculated dose that exceeds its correct dose by 50% or more and is administered to the subject will be considered an overdose and documented as an AE

The following events will not be identified as AEs in this study:

- Progression or exacerbation of the subject's underlying disease. However, clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction); however, the condition (the "triggering event") that leads to the procedure may be an AE
- Pre-existing conditions present or detected prior to the first dose of study drug that do not worsen

8.2.3 Assigning Attribution of AEs

The Investigator must attempt to determine the cause of each event. To ensure consistency of AE/SAE causality assessments, Investigators should apply the following guideline:

Related:	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Not Related:	The event is related to an etiology other than the investigational study drug (the alternative etiology must be documented in the study subject's medical record).

8.2.4 Classifying Action Taken with Study Drug

Classification	**Definition**
Dose Not Changed	Study drug dose not changed in response to the AE
Drug Interrupted	Study drug administration interrupted in response to an AE
Drug Discontinued	Study drug administration permanently discontinued in response to an AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt or withdraw treatment is possible.

8.2.5 Classifying AE Outcome

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/ Not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. “Fatal” should be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow up)

8.2.6 Documenting and Reporting AEs and SAEs

All SAEs that occur after obtaining informed consent through the last follow-up visit, regardless of causality, must be reported by the Investigator to the Sponsor’s designee for SAE reporting (see Study Manual for reporting specifics). In addition, all SAEs, including those that result in death, that occur after the completion visit and that are considered related to study drug(s) must be reported to the Sponsor's designee within 24 hours.

SAEs will be recorded on the Clinical Trials SAE Form using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the Investigator for severity, relationship to the investigational study drug(s) and possible etiologies. On the Clinical Trials SAE Form, relationship to study drug(s) will be assessed per the attribution guidelines in Section 8.2.3, and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution or stabilization and report to the Sponsor’s designee the outcome of the event using the SAE Form.

The Investigator is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form should be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available, to ensure timely reporting to Health Authorities.

The SAE Form should be sent to the Sponsor's designee using the cover sheet provided.

Aligos or its designees, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, and participating Investigators, in accordance with International Council for Harmonisation (ICH) Guidelines, and/or local regulatory requirements, as applicable.

8.2.7 Documenting and Reporting of Pregnancy

Subjects will be counseled to inform the Investigator of any pregnancy that occurs during study drug administration and for 3 months after the last dose of study drug(s).

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug administration must be permanently discontinued immediately. The Investigator must notify the Sponsor's Medical Monitor and Clinical Research Organization within 1 business day of the site's knowledge of the subject's (or partner's) pregnancy, by utilizing the Pregnancy Initial Report Form. The subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE, but the product of pregnancy could potentially be a SAE which necessitates the aforementioned follow-up.

8.3 Follow-up of AEs and SAEs

Follow all AEs (serious and non-serious) until resolution, the subject dies, the event stabilizes and is not expected to further resolve, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented. Aligos may request that the Investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

8.4 Sponsor's Review of AEs and SAEs

Aligos will maintain an ongoing review of all AEs and SAEs.

8.5 Special Safety Considerations

8.5.1 Management of Increases in ALT

Management of potential liver safety signals has been designed to ensure subject safety. The following guidance is consistent with FDA guidance for premarketing clinical evaluation on drug-induced liver injury (FDA 2009).

Definition of Baseline ALT Values

Baseline values for ALT will be defined as an average of all ALT values obtained between screening and baseline (Day 1).

New ALT Increases in Subjects with Baseline ALT ≤1.2× ULN

If a subject experiences a post-baseline increase in ALT to >3×ULN, subject should have a confirmatory ALT measurement (as well as AST, total and fractionated bilirubin, alkaline phosphatase, INR) performed within 24 hours of the result. Subjects should remain on study drug while confirmatory testing is being conducted. If the ALT increase is confirmed to be >3×ULN

and no other cause is immediately identified or apparent, the subject must be closely monitored (as described below) and the case should be carefully reviewed with the Sponsor's Medical Monitor and the SRC. Subjects must be monitored until abnormal liver biochemistry levels resolve, stabilize, or return to baseline values.

Discontinuation of study drug should occur if any of the following is observed at any time (*note*: based on confirmed ALT values):

- ALT >5×ULN
- ALT >3×ULN **and** (total bilirubin >2×ULN **or** INR >1.5) (*note*: in subjects with Gilbert's syndrome, direct bilirubin >2× baseline will be used instead)
- ALT >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

New ALT Increases in Subjects with Baseline ALT >1.2×ULN (Cohort 1 subjects only)

If a subject experiences a post-baseline increase in ALT >2× baseline, subject should have a confirmatory ALT measurement (as well as AST, total and fractionated bilirubin, alkaline phosphatase, INR) performed within 24 hours of the result. Subjects should remain on study drug while confirmatory testing is being conducted. If the ALT increase is confirmed to be >2× baseline and no other cause is immediately identified or apparent, the subject must be closely monitored (as described below) and the case should be carefully reviewed with the Sponsor's Medical Monitor and the SRC. Subjects must be monitored until abnormal liver biochemistry levels resolve, stabilize, or return to baseline values.

Discontinuation of study drug should occur if any of the following is observed at any time (*note*: based on confirmed ALT values):

- ALT ≥5× baseline or ≥500 U/L (whichever comes first)
- ALT ≥3× baseline or ≥300 U/L (whichever comes first) **AND** concomitant total bilirubin ≥5×ULN (direct bilirubin must also be ≥35% of the total bilirubin in subjects with suspected Gilbert's) or INR ≥1.5
- ALT ≥2× baseline **AND** appearance or worsening (from baseline) of symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%))

Close Monitoring for Suspected Drug-Induced Liver Injury

- Repeating liver enzymes (ALT, AST) and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.

- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

9.0 STUDY VARIABLES AND MEASUREMENTS

9.1 Safety Variables/Measurements

Safety evaluation will include AEs/SAEs, laboratory tests, ECG, vital signs, and physical examinations.

9.1.1 Adverse Events

AEs, including pretreatment events, will be recorded from the time of consent through the final follow-up visit. All AEs/SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.1.2 Clinical Laboratory Measurements

Clinical laboratory variables, including hematology, biochemistry, coagulation, urinalysis, and pregnancy testing, will be assessed at screening. Hematology, coagulation, biochemistry, and urinalyses testing will be evaluated periodically during the study as indicated in the Schedule of Events. A table of laboratory safety assessments to be evaluated during the study can be found in Appendix C.

9.2 PK Measurements

Blood samples will be collected from all subjects at specified times throughout the study for the determination of plasma PK parameters for ALG-097558 (and its metabolite ALG-097730) (timepoints specified in the Schedule of Events (Table 6)). Unbound plasma concentrations of ALG-097558 will be determined across at least 3 timepoints.

Plasma concentrations of ALG-097558 and its metabolite ALG-097730 will be quantified using a validated LC-MS/MS method. Unbound plasma concentrations will be quantified using a qualified equilibrium dialysis or ultra filtration followed by detection using a qualified LC-MS/MS method. All calculations will use the actual times recorded on the CRF. ALG-097558 and other metabolites (if applicable), plasma concentrations and computed PK parameters will be

listed by subject and summarized by cohort (mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum, number of observations), as appropriate. Individual and mean (by time) concentrations versus time will be plotted by treatment group on both linear and natural logarithm scales.

Analysis details will be described in the PK statistical analysis plan (SAP).

9.3 Prior and Concomitant Medications

Use of all medications and supportive therapy from within 28 days of the screening visit through study completion will be recorded. All concomitant medications will be mapped using the World Health Organization Drug Global Dictionary (WHO-DD).

10.0 STATISTICAL CONSIDERATIONS

10.1 General Considerations

Each cohort may be analyzed/summarized once all subjects in that cohort have completed the follow-up assessments.

A final analysis will be conducted once all subjects have completed all specified follow-ups (or discontinued early) and data have been cleaned and locked.

Interim analyses may be performed at the Sponsor's discretion for internal decision making, health authority interactions, publication purposes, etc.

A detailed description of all analyses that will be performed based on the safety data and PK data will be presented in a SAP before the database is locked for final analyses. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

Continuous data will be summarized by descriptive statistics, including number of subjects, arithmetic mean, standard deviation, standard error of the mean, median, and range (min.- max.). Categorical data will be summarized by the number and percentage of subjects.

Strategies for handling missing, unused, or spurious data will be specified in the SAP.

Baseline demographic and background variables will be summarized overall for all subjects.

Baseline is defined as the last available non-missing measurement/assessment collected prior to the first study drug administration, if not specified otherwise. Change from baseline values will be calculated as the difference between the value at a post-baseline visit and the baseline value for the specific endpoint.

Tables will be presented by cohort. All collected data will be included in the subject data listings. Screen failure data will not be included in any of the analyses.

10.2 Study Endpoints

Refer to Section 4.2 for primary, secondary and exploratory endpoints for the study.

10.3 Determination of Sample Size

Up to 16 subjects will be enrolled. In Cohort 1, 8 subjects with moderate hepatic impairment will be enrolled. In Cohort 2, 8 subjects without hepatic impairment will be enrolled, as defined in Section 5.7.2.

Since there is no formal statistical hypothesis testing, no formal sample size calculation has been performed. The proposed sample sizes for each study part are typical for studies of this nature and are deemed sufficient to evaluate the study objectives for this Phase 1 study.

11.0 STATISTICAL METHODS

11.1 Study Population

11.1.1 Subject Disposition

An accounting of all subjects over the course of the study will be reported. Enrollment (including eligibility), subject completion, and premature discontinuation or withdrawal will be summarized, along with the reason for discontinuation or withdrawal. Major protocol violations will be tabulated and summarized separately.

11.2 Analysis Sets

The following analysis sets are defined for each part of this study. The inclusion/exclusion of subject(s) from each of the analysis sets will be determined prior to the database lock for the study, and the reasons for exclusions will be documented.

11.2.1 Intention-to-Treat Set

All enrolled subjects will be included in the Intention-to-Treat Set. All baseline characteristics and disposition analyses will be conducted based on the Intention-to-Treat Set.

11.2.2 Safety Set

All subjects enrolled into the study who have received at least one dose of study drug, whether prematurely withdrawn from the study or not, will be included in the Safety Set. All safety analyses will be conducted based on the Safety Set.

11.2.3 Pharmacokinetic Set

Subjects who have received an ALG-097558 dose and have quantifiable concentration data will be included in the PK Set, as described in the SAP.

Where subjects experience issues which may affect exposure to study drug (e.g., emesis, dosing errors), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis. All subjects excluded from the PK population will be documented in the data listings.

All PK analyses will be conducted based on the PK Set.

11.3 Demographics and Baseline Characteristics

Demographic data (e.g., age, sex, ethnicity, height, body weight, BMI) will be summarized and presented in data listings. Baseline disease characteristics for Cohort 1 (e.g., Child-Pugh score) will also be included.

11.4 Safety Analysis

11.4.1 Adverse Events

All AE verbatim terms will be coded to the MedDRA System Organ Class and preferred terms. AEs will be summarized by the MedDRA System Organ Class and Preferred Terms. AE tables will present the number of patients and the number of events within each category. Subjects who experienced multiple AEs will only be counted once in each relevant category (System Organ Class and Preferred Terms), but all events will be included in the event frequencies.

Analyses will be based on TEAEs and AEs will be evaluated and documented using the grading scales defined in Appendix F.

Summaries (number and percentage of subjects) of TEAEs and SAEs by system organ class and preferred term will be provided by cohort. Treatment-emergent AEs will also be summarized by relationship to study drugs and severity. Separate listings and/or summaries may be provided for patients with SAEs, TEAEs leading to discontinuation of study drug and Grade ≥3 TEAEs.

11.4.2 Vital Signs, ECG, and Laboratory Assessments

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 (Appendix F) 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 Appendix F 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.

11.4.3 Concomitant Medications

All reported concomitant medications will be coded using WHO-DD.

Prior medications are defined as any medication where the use was stopped prior to the first study administration. Concomitant medications are defined as any medication that was used at least once after the first study drug administration. Medications that were stopped on the same date as the first administration will be analyzed as concomitant medications.

Concomitant mediations will be summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) Level 2 terms and by preferred name within the Anatomical Therapeutic Chemical term. Within each category, the number of subjects who used the medication (count and percentage) will be presented. Subjects who used the same medication on multiple occasions will only be counted once in the specific category (ATC or preferred name).

11.5 Pharmacokinetic Analysis

Samples at a single timepoint prior to and after dosing will be obtained as described in the Schedule of Events (Table 6).

The PK parameters for total and unbound ALG-097558 and the metabolite ALG-097730 will be determined by standard non-compartmental methods as appropriate. PK parameters include but not limited to AUCs, T_{max}, C_{max}, C_{min}, C_0 (predose), CL/F, Vz/F, and $t_{1/2}$.

The calculated values for all PK parameters will be tabulated by subject, by treatment and presented as graphs and by-subject listings. Computed PK parameters (primary and secondary) will be listed by subject and summarized by treatment group (mean, geometric mean, standard deviation, coefficient of variation, median, minimum, maximum, number of observations), as appropriate. PK parameters may be explored and the relationship between the measures of patient characteristics and PK parameters may be assessed graphically. Additional analyses or summaries may be considered, as appropriate. Individual and mean (by time) concentrations versus time will be plotted by treatment group on both linear and natural logarithm scales.

Details for statistical consideration for PK evaluation will be defined in the SAP.

11.6 Exposure-Response Analysis

Safety parameters may be subjected to exploratory exposure-response analyses as appropriate. ALG-097558 exposure versus safety parameters (e.g., liver function tests) may be subjected to an exploratory graphical analysis including various transformations to get a general overview, as appropriate.

Additional details for statistical consideration for PK/pharmacodynamic analysis will be defined in the SAP.

12.0 ADMINISTRATIVE CONSIDERATIONS

The Investigator and/or Sponsor, consistent with local regulatory practice, will submit this protocol, the informed consent, Investigator's Brochure, and any other relevant supporting information to the competent authority and appropriate IRB/IEC for review and approval prior to study initiation. A letter confirming IRB/IEC approval of the protocol and informed consent, a statement that the IRB/IEC is organized and operates according to Good Clinical Practice and the applicable laws and regulations, and financial disclosures (if applicable) must be forwarded to Aligos prior to screening subjects for the study. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, prior to the implementation of changes in this study.

12.1 Study Compliance

The study will be conducted in compliance with this protocol, principles of ICH Good Clinical Practice, Declaration of Helsinki, and all applicable national regulations governing clinical trials, and any relevant law, statute, declaration, decree, directive, legislative enactment, order, ordinance, regulation, rule or other binding instrument which implements any of the above or which otherwise relates to data protection, privacy or the use of personal data, in each case as applicable and in force from time to time, and as amended, consolidated, re-enacted or replaced from time to time (the "applicable data protection laws").

The Investigator and site staff must comply with the requirements of the applicable data protection laws with regards to the collection, storage, processing and disclosure of personal information and will uphold the applicable data protection laws' core principles. Access to personal data of subjects will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

12.2 Informed Consent and Protected Subject Health Information Authorization

A copy of the IRB/IEC-approved informed consent must be forwarded to Aligos for regulatory purposes. The Investigator or designee must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in ICH E6 Good Clinical Practice Guideline pertaining to informed consents, and other applicable national and local regulations governing informed consent, including applicable data

protection laws. Each subject must provide a signed and dated informed consent prior to enrollment into this study. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national subject privacy land data protection regulations (including applicable data protection laws), the Investigator or designee must explain to each subject prior to screening that for the evaluation of study results, the subject's protected health information and other personal data obtained during the study may be shared with Aligos and its designees, regulatory agencies, and IECs/IRBs. As the study Sponsor, Aligos will not use the subject's protected health information/personal data or disclose it to a third party without applicable subject authorization including such authorization contained in the signed ICF. The confidentiality of personal data will be preserved when the data are transmitted to third parties. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information and other personal data from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian and to ensure that no further personal and clinical data will be collected from the subject. Any personal and clinical data collected on the subject prior to withdrawal will be used in the analysis of study results, including as permitted by applicable data protection laws.

12.3 Subject Screening Log

The Investigator must keep a record that lists all subjects considered for screening in the study. For those subjects subsequently excluded, record the reason(s) for exclusion.

12.4 Case Report Forms

Study site personnel will complete CRFs designed for this study according to the completion guidelines that will be provided. An eCRF may be used for this study. Study site personnel will be trained and authorized to use the system in compliance with § 21 CFR Part 11 prior to recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the system.

Alternatively, if utilized, paper CRFs should be completed in black or dark blue ink. All corrections on paper CRFs will be made by drawing a single line through the information to be corrected, without obscuring it. All corrections will be initialed and dated (and explained, if necessary). Do not use "white-out" or obscuring correction fluid/tape to make changes.

The Investigator will ensure that the CRFs are accurate, complete, legible, and completed in a timely fashion. Where a subject exercises a data subject right under applicable data protection laws in relation to their personal data, the Investigator and study site personnel will cooperate to the extent necessary to ensure compliance with such a request under applicable data protection laws. Separate source records are required to support all CRF entries. The CRF is not to be used

to document data without prior written or electronic records. Case report forms should be completed for every subject enrolled in the study. At the study's conclusion, a PDF file will be created for each site containing their subjects' data submitted on eCRFs. In the event of an audit or regulatory authority inspection, copies of the eCRFs will be printed.

12.5 Study Monitoring Requirements

Representatives of Aligos or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff as well as any appropriate communications by web interface, mail, e-mail, videocall, or telephone. In countries where it is permitted, remote monitoring (source data verification) may occur to facilitate ongoing data review if an on-site visit is not able to be performed due to unavoidable restrictions and events. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to Quality Assurance reviews and/or audits under the Aligos Clinical Quality Assurance program.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. Where applicable, personal data of subjects will be protected by pseudonymization, i.e., the creation of coded, depersonalized data where the subject's identifying information is replaced by an unrelated sequence of characters.

However, because of the experimental nature of this study, the Investigator agrees to allow the IRB/IEC, representatives of Aligos, its designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

12.6 Retention of Records

The Investigator must retain a copy of all documents relating to this clinical trial for a minimum of 5 years after a marketing application is approved for the drug, unless Aligos notifies the Investigator in writing that study documents no longer need to be retained because a marketing application will not be filed. The Investigator must retain documents for a longer period, where so required by other applicable requirements, including under the applicable data protection laws. Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities and appropriate regulatory authorities. Any records (whether in electronic form or not) containing any personal data of the subjects shall be stored in a secure manner and in compliance with applicable data protection laws. Any linking code to pseudonymized data will be kept in a secure manner and in compliance with applicable data protection laws. The medical files of trial subjects shall be retained in accordance with national legislation and the maximum period permitted by the hospital, institution, or private practice. The Investigator is responsible for informing Aligos before any study-related documents are sent

offsite for archiving at the end of the trial. The investigator must receive written approval from Aligos before destroying documents.

12.7 Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations, including under applicable data protection laws) for additional research and to the extent the purpose of such research is compatible with the original purpose under which the subjects' personal data was collected. Samples will only be used to understand ALG-097558, to understand COVID-19, and/or biomarkers modified by COVID-19, to understand differential responses to ALG-097558, and to develop diagnostic tests/assays related to ALG-097558 and COVID-19. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

12.8 Confidentiality and Publication Policy

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.

By conducting this study, the Investigator affirms to Aligos that all study results and information furnished by Aligos will be maintained in strict confidence and not be used for any purposes except to conduct the study. Such information will be communicated to the Investigator's IRB/IEC under an appropriate understanding of confidentiality.

A published summary of the results of this study is, however, permissible in coordination with Aligos and is not inconsistent with the preceding affirmation of confidentiality. Any publication of data collected as a result of this study will be considered a joint publication by the Investigator(s) and appropriate Aligos personnel. Authorship, including order, will be determined by Aligos. Contribution of the author to the study design, enrollment, data review, and manuscript preparation and review will be considered when determining the order of authorship for multicenter studies. Aligos must receive a copy of any presentation, manuscript, or abstract for review at least 60 days prior to public presentation or submission for publication. Any publication outside of this agreement is not permitted.

12.9 Conduct of Study and Protection of Human Subjects

The Principal Investigator must ensure the following (unless Sponsor is required per local regulations, including under applicable data protection laws):

1) He or she will personally conduct or supervise the study.
2) His or her staff and all persons who assist in the conduct of the study are under an obligation of confidentiality in relation to the subject's personal data and clearly understand their responsibilities and have their names included in the Study Staff Signature and Delegation of Authority log. The Investigator will sign the authorization log whenever it is updated with new responsibilities or staff membership.
3) The study is conducted according to the protocol and all applicable regulations.
4) The protection of each subject's rights and welfare is maintained.
5) Subject to applicable data protection laws, signed and dated ICF with permission to use protected health information and other personal data are obtained from each subject prior to conducting study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information and/or personal data, the Investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no such further data be collected from the subject, subject to applicable data protection laws.
6) The consent process is conducted in compliance with all applicable regulations and applicable data protection laws and privacy acts.
7) The IRB/IEC and local competent authority comply with applicable regulations and conduct initial and ongoing reviews and approvals of the study.

8) Any amendment to the protocol is submitted promptly to the competent authority and IRB/IEC.
9) Any significant protocol deviations are reported to Aligos, the local competent authority and the IRB/IEC according to the guidelines at each study site.
10) All Safety Reports are submitted promptly to the local competent authority and IRB/IEC in accordance with the institution's internal policy.
11) All SAEs are reported within 24 hours of knowledge of the event, and to the local competent authority and the IRB/IEC.

12.10 PREP Act

The trial therapeutic 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 US 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 extended on May 23, 2023.

The PREP Act also established the Health Resources and Services Administration 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 1 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.

13.0 REFERENCES

13.1 Literature References

[redacted]

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328-357. doi: 10.1002/hep.29367. Epub 2017 Sep 29.

de Lucia C, Eguchi A, Koch WJ. New insights in cardiac β-adrenergic signaling during heart failure and aging. Front Pharmacol 2018;9:904. https://doi.org/10.3389/fphar

[redacted]

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med 2022;386:1397-408. doi: 10.1056/NEJMoa2118542

Hopkins SR, Bogaard HJ, Niizeki K, et al. β-Adrenergic or parasympathetic inhibition, heart rate and cardiac output during normoxic and acute hypoxic exercise in humans. J Physiol 2003;550(2):605–16. doi: 10.1113/jphysiol.2003.040568

Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis 2021;72(9): e206-e214.

[redacted]

Thakur B, Dubey P, Benitez J, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep 2021;11:8562.

Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81(2):e16-e25.

13.2 Regulatory Guidance and Online References

Center for Disease Control and Prevention (CDC). COVID-19 Treatments and Medications. https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html. Updated Dec. 5, 2022b.

Center for Disease Control and Prevention (CDC). Symptoms of COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Updated Oct. 26, 2022a.

Center for Disease Control and Prevention (CDC). Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Updated 9 February 2023. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

EMA Guideline on the investigation of drug interactions. 21 June 2012. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf

FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Updated September 2022.

FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (clinical pharmacology May 2003)

FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009.

FDA News Release. FDA Approves First Treatment for COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. 22 October 2020.

National Institute on Alcohol Abuse and Alcoholism (NIAAA) webpage What Is a Standard Drink? Available at: https://www.niaaa.nih.gov/what-standard-drink

National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/. Updated 30 Jan 2023. Accessed: 8 February 2022

National Institutes of Health (NIH). COVID-19 treatment guidelines: Table 2a. Therapeutic management of nonhospitalized adults with COVID-19. Last Updated: 28 December 2022. Available at: https://www.covid19treatmentguidelines.nih.gov/tables/management-of-nonhospitalized-adults-summary/

National Institutes of Health (NIH). Drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/. May 13, 2022b.

US Department of Health and Human Services (HHS). Combat Covid webpage. Who is at high risk for serious COVID-19? Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

WHO Coronavirus (COVID-19) Dashboard. Available at https://covid19.who.int/.

WHO Coronavirus disease (COVID-19)–Symptoms. Available at https://www.who.int/health-topics/coronavirus#tab=tab_3.

WHO. COVID-19–China. Available at https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON233.

WHO. Therapeutics and COVID-19. Living Guideline. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.4. Accessed 13 January 2023.

14.0 APPENDICES

Appendix A. Investigator Signature Page

Study Acknowledgment

Protocol No.	ALG-097558-702
Study Title:	A Phase 1 Non-Randomized, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of ALG-097558 in Subjects with Moderate Hepatic Impairment and in Healthy Subjects with Normal Hepatic Function
Version:	3.0
Date:	30 September 2024

This protocol has been approved by Aligos Therapeutics. The following signature documents this approval:

[redacted]

Date

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined in Section 12.9, Conduct of Study and Protection of Human Subjects and will make every effort to complete the study within the time designated.

Principal Investigator Name (Printed)

Signature

Date

Site Name

Appendix B. Prohibited Medications

Note: The following table is not an exhaustive list. The list of prohibited medications is subject to change based on emerging information related to the study drugs or other medications (e.g., new information from the medical literature). The most up-to-date list of prohibited medications may be found in the "CYP Enzyme- and Transporter System-Based Clinical Substrates, Inhibitors, or Inducers' table (available on the FDA website at: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems).

The use of prohibited medication may result in discontinuation of study drug. Subjects who discontinue study drug due to use of a prohibited medication will be followed up as outlined in Section 5.8.6. The Sponsor should be contacted in case of any questions.

Sensitive CYP2C8 and CYP2B6 Substrates
Repaglinide, rosiglitazone, paclitaxel, bupropion
Strong CYP3A4 Inhibitors Atazanavir, clarithromycin, itraconazole, posaconazole, voriconazole, nefazodone, nelfinavir
Moderate CYP3A4 Inhibitors Aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, erythromycin, fluconazole, imatinib, isavuconazole, verapamil
Strong CYP3A4 Inducers Rifampin, phenytoin, carbamazepine, St. John's Wort
Moderate CYP3A4 Inducers Bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib
P-gp Inhibitors Amiodarone, clarithromycin, cobicistat, cyclosporine, dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib, lopinavir and ritonavir, quinidine, ranolazine, saquinavir and ritonavir, verapamil

Appendix C. Clinical Laboratory Evaluations

<table>
<tr><th colspan="2">Chemistries:</th><th>Hematology:</th></tr>
<tr><td>Albumin
Amylase
Bicarbonate
Urea Nitrogen (BUN) or Urea
Calcium
Chloride
Total Cholesterol
HDL and LDL
Creatinine
Creatine kinase
Glucose
Lipase
LDH
Magnesium
Phosphorus
Potassium
Sodium
Total protein
Triglycerides
Uric acid</td><td>Liver function tests:
• ALP
• ALT
• AST
• Total bilirubin
• Direct/Indirect bilirubin</td><td>Hematocrit
Hemoglobin
Platelets
Erythrocytes (RBC)
Reticulocytes
Leukocytes (WBC)

WBC differentiation (% & absolute):
Basophils, Basophils/Leukocytes
Eosinophils, Eosinophils/Leukocytes
Lymphocytes, Lymphocytes/Leukocytes
Monocytes, Monocytes/Leukocytes
Neutrophils, Neutrophils/Leukocytes</td></tr>
<tr><th colspan="2">Urinalysis:</th><th>Coagulation:</th></tr>
<tr><td colspan="2">Color
Specimen Appearance
pH
Specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult Blood
Protein
Urobilinogen
Microscopic (including RBCs and WBCs) – reflex test only</td><td>Prothrombin time/International Normalization Ratio (INR)
PTT</td></tr>
</table>

<table>
<tr><th>Drug Screen (Urine):</th><th>Smoking Screen:</th><th>Other Tests:</th></tr>
<tr><td rowspan="2">Methadone
Amphetamine
Barbiturate
Cocaine
Opiates
Benzodiazepine</td><td></td><td rowspan="2">Hepatitis A:
• Hepatitis A virus IgM antibody (HAV IgM)
Hepatitis B:
• Hepatitis B virus surface antigen (HBsAg)
• Hepatitis B core antibody (HBcAb)
• HBV DNA [a]
Hepatitis C:
• Hepatitis C virus antibody (HCV Ab) and/or HCV RNA
Hepatitis E [b]:
• HEV IgM or RNA (by PCR)
HIV:
• HIV-1/2 antibody
• HIV-1 RNA [a]
• CD4+ T cell count [a]</td></tr>
<tr><td>Alcohol Screen (Urine):
Ethanol</td></tr>
<tr><td colspan="3">Females only:</td></tr>
<tr><td colspan="3">Choriogonadotropin Beta Pregnancy Test (serum and urine)
FSH (Postmenopausal women only)[c]</td></tr>
</table>

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; HIV-1/2Ab=human immunodeficiency virus antibody; LH=luteinizing hormone; RBC=red blood cell count; WBC=white blood cells.
Notes:

[a] For Cohort 1 subjects only, to confirm stable disease and/or eligibility.

[b] Hepatitis E testing only required for subjects who have lived in or visited Hepatitis E endemic areas.

[c] FSH is taken at screening only in women (postmenopausal women).

Appendix D. Criteria for Potentially Clinically Significant ECG and Vital Sign Abnormalities

	ECG Parameter [b]			
Abnormality Code	**HR (bpm)**	**PR (ms)**	**QRS (ms)**	**QT_c [a] (ms)**
Actual Value				
Abnormally low	<40	Not applicable	–	–
Abnormally high	>100	>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
	Vital Sign Parameter [b]		
Actual Value	**Pulse (bpm)**	**DBP (mmHg)**	**SBP (mmHg)**	
Abnormally low	<40	<45	≤90	
Level I	–	>90 to <100	>150 to <160	
Level II	–	≥100 to <110	≥160 to <180	
Level III	–	≥110	≥180	
Abnormally high	>100	–	–	

ΔQTc=change from baseline QTc; bpm=beats per minute; DBP=diastolic blood pressure; ECG=electrocardiogram; HR=heart rate; mmHg=millimeters of mercury; ms=millisecond; PR=PR interval; QRS=QRS interval; QTc=QT interval corrected for heart rate; SBP=systolic blood pressure.

[a] Definition of absolute QTc parameters is based on ICH E14.

[b] Classification of AEs related to these cardiovascular parameters will be based on the Division of AIDS (DAIDS) grading scale v2.1 (July 2017).

Appendix E. Contraceptive and Barrier Guidance

Definitions Appendix

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- Premenarchal

A premenarchal state is one in which menarche has not yet occurred.

- Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause, confirmed by a high follicle-stimulating hormone (FSH) level in the postmenopausal range at screening.

- Permanently sterile

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (e.g., a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives [a,b] Allowed During the Study Include:

USER INDEPENDENT

Highly Effective Methods That Are User Independent

Failure rate of ≤1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion/ligation

- Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT

Highly Effective Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [b]
  - oral
  - transdermal
  - intravaginal
  - injectables
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY
(not considered to be highly effective: failure rate of >1% per year)

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide [c]
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) [c]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method

[a] Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

[c] Male condom and female condom should not be used together (due to risk of failure with friction).

Appendix F. Grading the Severity of Adverse Events

Adverse events will be graded, by default, using the Division of AIDS (DAIDS) scale v2.1 (July 2017), which will be provided.

For AEs that are not specifically identified in the DAIDS grading table, grading by the Principal Investigator should be based on specific findings related to the parameter of interest and the subject's overall clinical profile. Refer to following table for guidance on grading of AEs *not specifically* identified in a DAIDS grading table, as adapted from DAIDS (see "Instructions for Use").

Grading of AEs Not Specifically Identified in a DAIDS Grading Table

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Clinical adverse event **NOT** identified elsewhere in the DAIDS grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Note: All deaths related to an AE are to be classified as Grade 5.

Additionally, for purposes of data summarization and analysis, when a laboratory result cannot be graded using the DAIDS scale, the following flags will be used to characterize that abnormality.

Flag Scale for Laboratory Abnormalities Without a DAIDS Grade

Laboratory parameter is	
Abnormal High	**Abnormal Low**
>1-<2× ULN	<1-≥0.9×LLN
≥2-<5× ULN	<0.9->0.7×LLN
≥5-<10× ULN	≤0.7->0.5×LLN
≥10× ULN	≤0.5×LLN

LLN=lower limit of normal; ULN=upper limit of normal.