ARN-75039 CAPSULES

PROTOCOL ARN-75039-101

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-PART (SINGLE-ASCENDING DOSE AND MULTIPLE-ASCENDING DOSE) STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ARN-75039 WHEN ADMINISTERED BY THE ORAL ROUTE IN HEALTHY ADULT SUBJECTS

Version 6.1 (12 December 2024)

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Arisan Therapeutics, Inc.

Sponsor's Authorized Officer: Ken McCormack, PhD

Arisan Therapeutics, Inc.	Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ARN-75039. I have read Protocol ARN-75039-101 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of Arisan and the IRB, except where necessary to eliminate an immediate hazard to the study subject.

I agree to comply with the International Council for Harmonisation Tripartite Guideline on Good Clinical Practice and applicable regulations of the Food and Drug Administration.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Protocol v6.1	12 December 2024
Protocol v6.0	22 November 2024
Protocol v5.0	08 July 2024
Protocol v4.2	08 May 2024
Protocol v4.1	12 March 2024
Protocol v4.0	29 December 2023
Protocol v3.0	27 June 2023
Protocol v2.1, Amendment 2	09 January 2023
Protocol v2.0, Amendment 1	23 November 2022
Original Protocol v1.1	24 October 2022

Amendment 6.1, 12 December2024

Overall Rationale for the Amendment:

The Sponsor has, as reflected in the Schedule of Assessments Table 3 and text throughout the protocol, and has also made administrative updates (not requiring a rationale):

Section # and Name	Description of Change	Brief Rationale
Study Design, Globally to corresponding text	Included serum tryptase and plasma histamine laboratory assessments to test for mast cell activation in MAD Cohort 11.	To explore mast cell activation as potential mechanism of action in previously observed AEs and provide improved safety monitoring.
Study Design, Globally to corresponding text	Included the conduct of the Active Stand Test (also known as the NASA 10-Minute Lean Test) on Day -1.	To explore possible orthostatic intolerance and to improve safety monitoring.

Abbreviations: AE = adverse event; MAD = multiple ascending dose; NASA = National Aeronautics and Space Administration.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Clinical Study Leader	Karrielynn Gerlach	Spaulding Clinical Research, LLC 525 S Silverbrook Dr. West Bend, WI 53095 Telephone: 920-517-2167
Responsible Physician	Dr. Stephanie Post	Spaulding Clinical Research, LLC 525 S Silverbrook Dr. West Bend, WI 53095 Telephone: 920-251-1769
Drug Safety Physician	Dr. Shaun Merchant	Safe Harbor Pharmacovigilance Telephone: 347-653-9989
24-Hour Emergency Contact	N/A	Telephone: 800-597-4507 Telephone: 855-622-8100 (24-hour urgent question/care)

Abbreviations: LLC = limited liability corporation; N/A = not applicable.

SYNOPSIS

Title of Study Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Two-Part (Single-Ascending Dose and Multiple-Ascending Dose) Study to Assess the Safety, Tolerability, and Pharmacokinetics of ARN-75039 when Administered by the Oral Route in Healthy Adult Subjects

Protocol Number: ARN-75039-101

Name of Sponsor Company: Arisan Therapeutics

Name of Investigational Product: ARN-75039 for oral administration

Phase of Development: Phase 1

Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
• To assess the safety and tolerability of single and multiple doses of ARN-75039 when administered by the oral route at escalating dose levels in healthy adult subjects.	• Type and frequency of treatment-emergent adverse events (TEAEs). • Type and frequency of treatment-emergent serious adverse events (TESAEs). • Type and frequency of study drug-related Grade > 1 TEAEs. • Type and frequency of changes in clinical laboratory values, electrocardiograms (ECGs), colonic transit time (biomarker), physical examinations, and vital signs.
Secondary Objectives	**Secondary Endpoints**
• To determine the recommended Phase 2 dose (RP2D) and regimen of ARN-75039 capsules.	• RP2D and regimen of ARN-75039 capsules.
• To assess the PK of single and multiple doses of ARN-75039 when administered by the oral route. • To assess the effect of food on the PK of a single oral administrations ARN75039.	• PK parameters of ARN-75039 capsules, including but not limited to: o Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{0-t}). o Appropriate partial AUCs: Area under the concentration-time curve from time 0 to the end of dosing interval ($AUC_{0-\tau}$) or alternative partial AUCs as appropriate to the dosing regimen (eg, AUC_{0-10} for BID, if applicable, and AUC_{0-24} for QD) to properly address the study objectives o Area under plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$). o Maximum observed plasma concentration (C_{max}). o Time to reach C_{max} (t_{max}). o Half-life ($t_{1/2}$). o Apparent clearance after extravascular administration (CL/F). o Apparent volume of distribution during the terminal phase after extravascular administration (V_z/F).

Study Design:

ARN-75039-101 is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and PK of escalating single and multiple doses of ARN-75039 when administered by the oral route in healthy adult subjects. Pharmacokinetic analysis of hydroxypropyl methylcellulose (HPMC) capsules filled with neat ARN-75039 (10 mg) was assessed in dogs under both fed and fasted conditions. Mean maximum plasma exposures (C_{max}) and AUC_{0-24} were 5.2- and 8.8- fold higher in fed dogs versus fasted dogs. Therefore, it was decided to dose volunteers under fed state conditions. Within each cohort, the first 2 subjects will be randomized 1:1 to receive ARN-75039 capsules or placebo. After Medical Monitor review of the first 3 days of blinded safety in the SAD part and 8 days of blinded safety in the MAD part (following completion of the Sitzmark® test in MAD part only), an additional 6 subjects will be randomized in a 5:1 (active: placebo) ratio. Following completion of dosing in the SAD part of the study, a planned interim analysis was performed to help determine dose levels in the MAD part of the study. A description of the study cohorts including the study part, dose, number of subjects, and status follows:

Study Part	Cohort	Meal	Dose	ARN-75039 (Number of Subjects)	Matching Placebo (Number of Subjects)	Status
1: SAD	1	Fed	30 mg	6	2	Completed
	2	Fed	100 mg	6	2	Completed
	3	Fed/Fasted	300 mg (fasted cohort added)	8	2	Completed
	4	Fed	600 mg	6	2	Completed
	5	Fed	1200 mg	6	2	Completed
	6	Fed	2000 mg (up to 2400 mg planned)	6	2	Completed
2: MAD	7	Fed	Day 1: 36 and 24 mg doses Day 2: 24 mg BID Days 3–10: 12 mg BID	6	2	Completed
	8	Fed	Day 1: 75 and 50 mg doses Day 2: 50mg BID Days 3–10: 25 mg BID	6	2	Completed
	9	Fed	Day 1: 150 and 100 mg doses Day 2: 100 mg BID Days 3–10: 50 mg BID	6	2	Completed
	10	Fed	Day 1: 240 and 160 mg doses Day 2: 160 mg BID Days 3–10: 80 mg BID	6	2	Completed
	11	Fed	Day 1: 360 and 240 mg doses Day 2: 240 mg BID Days 3–10: 120 mg BID	6	2	Planned

Abbreviations: BID = twice daily (*bis in die*); MAD = multiple ascending dose; SAD = single ascending dose.
Note: BID doses will be administered approximately 10 hours apart.

In Part 2 (MAD), dose regimens include twice daily (BID) dosing and have been designed generally as follows: On Day 1 an initial 3× (relative to maintenance dose) loading dose will be administered followed by a 2× dose. On Day

2, 2× (relative to maintenance dose) BID dosing will be administered. On Days 3–10, BID administration of a 1× maintenance dose will be provided. The dose regimens in Cohorts 7–11 are provided in the table above. The dose levels and dosing intervals in the MAD cohorts have been determined based on the safety and PK of ARN-75039 demonstrated in the SAD part of the study along with non-clinical general toxicity findings observed in rats and dogs, with the objective of determining the RP2D.

An overview of the conduct of each study part follows:

- **Part 1 SAD:** The SAD part of the study is the first-in-human (FIH) study of ARN-75039. Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following a 3-day safety observation period with the approval of the Medical Monitor. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through study Day 8. Up to 5 SAD cohorts are planned, comprising a total of approximately 40 subjects to be administered study drug in Part 1 of the study (30 assigned to ARN-75039 and 10 assigned to placebo).

  A cohort of subjects in the SAD portion of the study may be enrolled to receive a second dose of study drug in the fasted state following an appropriate washout period, with each dose separated by at least 15 days, in order to assess food effect (including relative bioavailability); the dose level utilized for the food effect cohort(s) will be selected based on the demonstration of adequate safety at the next higher dose level, as assessed by the Safety Monitoring Committee (SMC). The dose level utilized for the food effect cohort(s) will be selected by the SMC based on review of safety data from completed SAD, and as applicable, MAD, cohorts.
- **Part 2 MAD:** The MAD part of the study will be initiated after the safety and PK data from the SAD part of the study have been reviewed by the Food and Drug Administration (FDA) and the Sponsor and FDA have determined that it is safe to proceed. The MAD part of the study will utilize BID oral doses of ARN-75039 for a total of 10 days for each subject. The proposed doses and dose regimen have been determined based on the safety and PK results from the SAD part of the study and safety margins (ranging from 50- to 8-fold) of predicted $AUC_{0\text{-}24}$ for the proposed dose regimen and mean (both sexes) $AUC_{0\text{-}24}$ of the rat no observed adverse effect level (NOAEL) at 50 mg/kg. Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following an 8-day safety observation period during continuous oral dosing. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through Day 8. Up to 5 MAD cohorts are planned , comprising a maximum total of approximately 40 subjects to be treated in Part 2 of the study (30 ARN-75039 and 10 placebo). Additional subjects may be enrolled to compensate for early terminations or at the discretion of the Sponsor.

For both the SAD and MAD portions of the study, the occurrence of at least 2 study drug-related Grade > 1 TEAEs in subjects receiving ARN-75039 in any dose cohort will result in convening the SMC to determine whether dosing should be continued or terminated at that dose.

Written informed consent for study participation will be obtained before any study-related procedures or assessments are performed. All potential subjects will be screened for potential participation, and those meeting all eligibility criteria will be offered participation in the study.

Subject participation in the study will be conducted in the following 3 defined periods:

- **Screening Period:** The Screening Period begins when the informed consent form (ICF) is signed. During this period, subjects will undergo baseline assessments to determine eligibility for study participation. The Screening Period duration will be up to 35 days; it will end after all evaluations required to meet eligibility have been completed. If a subject meets all eligibility criteria, they will be offered enrollment into the study.
- **Treatment Period:** The Treatment Period will begin on Day 1 with randomization and administration of the first dose of study drug (ARN-75039 or placebo). The Treatment Period has a duration of 1 day for the SAD part of the study and 10 days for the MAD part of the study.

During the Treatment Period, 1 dose of study drug will be administered in the SAD part of the study; the number of doses and dosing schedule in the MAD part of the study are summarized in Table 6. The last MAD dose will be administered on Day 10.

In the food effect cohort(s), subjects will receive the first study drug dose on Day 1 followed by a second dose on Day 15 or thereafter, with the first administered under fed conditions and the second administered under fasted conditions.

Subjects will have periods of residency at the study site in each part of the study; residency during the SAD part will occur from Day -1 to Day 4 following first study drug dose and residency during the MAD part will occur from Day -1 to Day 11 (approximately 24 hours following the final study drug dose). (Subjects will be discharged after collection of the 24-hour post-dose PK sample.) In the food effect cohort(s), residency will occur from Day -1 to 4 around each study drug dose administration. Subjects will return to the study site for follow-up evaluations according to the Schedule of Assessments (SOA) during the Treatment Period (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort).

After completing the Treatment Period, subjects will enter the Safety Follow-up Period.

- **Safety Follow-up Period:** The Safety Follow-up Period will have a duration of 14 days for the SAD part of the study and 29 days for the MAD part of the study, culminating with an End-of-study (EOS) visit. For subjects who withdraw from the study prematurely, the EOS visit is to be conducted within 7 days after the last study drug dose.

Safety will be assessed at each study visit, and PK assessments will be conducted at specific time points per the SOA. Subjects who receive ≥ 1 dose of study drug will be encouraged to complete all study visits. If subjects terminate early from the study, they will be asked to return to the study site to complete the EOS Visit within 7 days after withdrawal from the study.

If a subject has a study drug-related Grade greater than 1 TEAE during the Treatment Period, study drug dosing will be discontinued for that subject. These subjects will not be replaced. If a subject has a study drug-related of Grade 1 TEAE during the Treatment Period, study drug dosing may also be discontinued for that subject per the Investigator's discretion. However, these subjects may be replaced at the Sponsor's discretion. It is recommended for subjects whose treatment was discontinued due to TEAEs to remain in the study to complete the study visits through the EOS visit for safety follow up purposes. If a subject terminates early for a reason unrelated to study procedures, the subject may be replaced.

Study drug dose level modifications or dosing administration deviations outside the protocol-specified windows are not permitted during the Treatment Period.

The SMC will periodically review all available clinical, GI transit biomarker, ECG, and laboratory data during the study. The SMC will convene and make recommendations regarding cohort advancement and study continuation, discontinuation, or modification.

Individual, Dose Escalation, and Study Stopping Rules

The RP2D is defined as the ARN-75039 dose demonstrating an appropriate safety, PK, and benefit/risk profile to advance into later phase development.

Dosing of ARN-75039 will be permanently discontinued in a subject if any of the following occurs:

- Subject experiences any study drug-related Grade > 1 TEAE
- Subject experiences any study drug-related Grade > 1 adverse event of special interest (AESI)
- Subject withdraws consent
- Subject becomes pregnant
- Subject is unable to comply with the protocol requirements
- Sponsor terminates the study
- Study dosing cessation is mandated by a regulatory authority

Dose escalation stopping rules will be used to determine whether or not investigation of a higher dose level will proceed per protocol. If 2 or more subjects receiving ARN-75039 experience a study drug-related Grade > 1 TEAE in a single cohort, further enrollment to the respective dose cohort will be stopped, and all study drug administration may be suspended, pending SMC evaluation of all available safety and PK data. After its evaluation, the SMC may recommend study continuation (with or without modification) or termination of dose escalation; the SMC may also recommend de-escalation to lower doses. If dose escalation is terminated for safety reasons, the next-lower dose may be declared the highest tolerable dose. Alternatively, an additional cohort at an intermediate dose may be added to better define the highest tolerable dose. The SMC will also evaluate the PK profile of ARN-75039, when available, to determine if a threshold exposure associated with potential anti-viral activity has been achieved which might correspond to the RP2D.

The study may be stopped at the discretion of the sponsor based on recommendations of the SMC. In all cases, all necessary measures will be taken to ensure appropriate safety follow-up of all subjects in the trial.

Number of Subjects Planned:

- In Part 1 (SAD), 5 cohorts of 8 subjects are planned (40 adult subjects: 30 ARN-75039 and 10 placebo) with an additional optional cohort (up to 8 additional adult subjects).
- In Part 2 (MAD), 5 cohorts of 8 subjects (40 adult subjects: 30 ARN-75039 and 10 placebo) are planned.

Study Duration:

- Part 1 (SAD): Approximately 6 weeks for each subject [approximately 9 weeks for subjects in the food effect cohort, if initiated].
- Part 2 (MAD): Approximately 10 weeks for each subject.

Eligibility:

Subjects will be required to meet all of the following inclusion criteria and none of the exclusion criteria in order to be eligible for study enrollment; the Sponsor will attempt to reach an overall preferred combined target enrollment goal of ≥30% and ≤50% African American and/or West African adult subjects to help assess potential population differences in safety, tolerability and PK in the primary clinical population.

Re-Screening Criteria:

In the event that a subject's screening laboratory value is outside the acceptable range, the laboratory test can be repeated once, and if the repeat value is within the acceptable range, the subject can be considered eligible for the study. In the event that a subject fails to meet the overall screening criteria, the subject may repeat the overall screening process once, and if the subject then meets all eligibility criteria, the subject will be considered eligible to enter the study.

Inclusion Criteria:

Subjects meeting all the following criteria are eligible for study participation:

1. Is male or female, age 18 to 55 years, inclusive, at Screening.
2. Body mass index (BMI) between 18.5 and 35 kg/m^2, inclusive, at Screening.
3. In good general health, determined by no clinically significant findings in the opinion of the Investigator from medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratory findings, and vital signs at Screening and Day -1 or 1.
4. Hemoglobin, hematocrit, white blood cell count, absolute neutrophil count, and platelet count results within the laboratory reference range at Screening or **without clinically significant abnormalities in the opinion of the Investigator**; subjects with Gilbert's disease with associated abnormalities of liver function tests are eligible for enrollment. Tests may be repeated at the discretion of the Investigator to confirm abnormalities.
5. Estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology

Collaboration (CKD-EPI) equation of ≥ 80 mL/min/1.73m^2 at Screening.

6. Females of childbearing potential must practice effective contraception per national regulatory guidelines for clinical trials from Screening, throughout the study, and for 28 days after the EOS visit.
7. Females of childbearing potential must have a negative pregnancy test at Screening and within 24 hours prior to dosing of study drug; for post-menopausal subjects, a blood sample will also be tested for follicle stimulating hormone (FSH) to confirm post-menopausal status (as verified by an FSH of ≥40). Surgically sterile females are eligible; however, proof via medical records will be required.
8. Males must agree to not donate sperm and/or to use condoms during sexual intercourse from the time of the first study drug administration and for 90 days following the last dose of study drug, and females must agree not to donate eggs from the time of the first study drug administration and for 60 days following the last dose of study drug.
9. Must be willing and able to comply with measures to avoid photosensitivity reactions (i.e., avoidance of outdoor sun exposure and tanning; consistent use of long sleeve shirts, long pants, hats, and sunglasses; consistent use of SPF 75 or greater sunscreen when outdoors) from Day 1 through Day 8 in Part 1 and through Day 25 in Part 2.
10. Able to provide informed consent.
11. Willing and able to comply with this protocol and be available for the entire duration of the study.

Exclusion Criteria:

Subjects meeting any of the following criteria are not eligible for study participation:

1. Any clinically significant underlying illness in the opinion of the Investigator.
2. Poor venous access.
3. Inability to ingest all capsules of a multi-capsule dose within 5 minutes of ingestion of the first capsule.
4. Prior exposure to ARN-75039.
5. Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening; subjects with adequately treated HCV are eligible for enrollment.
6. Positive test for SARS-CoV-2 infection on Day -1.
7. Consumption of Seville oranges, grapefruit or grapefruit juice within 72 hours prior to Day 1 or during the study.
8. History of drug or alcohol abuse within 1 year of Screening in the opinion of the investigator, or a positive test for drugs of abuse or alcohol at Screening or Day -1.
9. Use of any prescription or over-the-counter (OTC) medications, including food supplements, vitamins, herbal medications (e.g., St. John's wort), and cannabis, with the exception of contraceptive medications and as needed (prn) acetaminophen or paracetamol (not exceeding 2 grams/day) within 7 days prior to study drug administration and through the EOS visit.
10. History of malignancy, except adequately treated basal cell carcinoma or in situ carcinoma of the uterine cervix.
11. Smoking greater than 20 cigarettes, cigars, cigarillos or E-cigarettes per week in the 3 months prior to study drug administration or during the study.
12. Any female who is pregnant or breastfeeding, or any female who is planning to become pregnant during the study and safety follow-up period.
13. Any reason or condition that, in the investigator's opinion, may compromise study participation, present a safety risk to the subject, or may confound the interpretation of the study results.
14. A QT duration corrected for heart rate by Fridericia's formula (QTcF) > 450 millisecond (msec) based on either single or averaged QTcF values of triplicate ECGs obtained over a 3-minute interval (at Screening).
15. Blood product donation within 30 days before Screening.
16. Unwilling to consume breakfast and dinner on study drug administration days.

17. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 -half-lives of the prior investigational agent (whichever is longer) or plans to enroll in another investigational device or drug study during the course of this study.

Part 2 (MAD) only:

18. History of:
    a) Structural abnormality of the gastrointestinal (GI) tract or a disease or history of a condition that can affect GI motility
    b) Inflammatory bowel disease (even if treated and currently in remission)
    c) Diverticulitis or any other chronic condition such as chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, lactose intolerance that can be associated with abdominal pain or discomfort and could confound the assessments in this trial.
    d) Chronic idiopathic diarrhea
    e) Formally diagnosed colonic inertia or conditions that can be associated with constipation: pseudo-obstruction, colonic inertia, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis, lower tract evacuation disorders, functional outlet delay (e.g., rectal prolapse, anismus, etc.)
19. Current active peptic ulcer disease (i.e., disease that is not adequately treated or stable with therapy.)
20. Potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis.)
21. Subject currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia or any unexplained anemia, or weight loss) or systemic signs of infection or colitis.
22. Subjects who do not expel at least 80% (19 or more) of the markers after the Sitzmarks® colonic transit test administered during the screening period.
23. History of chronic/generalized pruritus and/or severe skin rash of unknown origin
24. Subjects diagnosed with Type 1 or Type 2 diabetes, or with a blood glucose value > 125 mg/dL during screening period.

Investigational Products, Dosage, and Mode of Administration:

Study drug is to be administered in the fed state, with subjects served a meal approximately 30 minutes prior to the scheduled study drug dose. Study drug will be administered with 240 mL or the smallest amount of water needed to swallow all the capsules.

If the food effect of ARN-75039 is explored, the second dose will be administered to subjects in this cohort study drug dose will be administered at the study site after an overnight fast of at least 10 hours. Water will be allowed for up to 2 hours prior to dosing, then restricted until 2 hours post-dose, with the exception of water taken (up to 240 mL) with capsule administration

ARN-75039 will be supplied to the clinical site as neat drug substance. The drug product will be prepared by the onsite pharmacist or designee by dispensing the specified weight of drug substance and encapsulating it in a hydroxypropyl methylcellulose (HPMC) capsule prior to dosing. ARN-75039 drug substance should be stored at 15–25°C.

Refer to the Pharmacy Manual for details.

Reference Product:

ARN-75039 capsule matching placebo will be orally administered. The placebo will be prepared by the onsite pharmacist or designee by dispensing the specified weight of placebo corresponding to the dose of ARN-75039

within the same cohort and encapsulating it in an HPMC capsule prior to dosing.

Refer to the Pharmacy Manual for details.

Statistical Methods:

This is a Phase 1 study; as such, none of the endpoints are sufficiently powered to demonstrate a robust difference between cohorts. The cohort size has been selected in accordance with standard designs for Phase 1 assessments of safety, tolerability, and PK.

The primary analysis will describe the incidence of adverse events and laboratory abnormalities. Adverse events will be coded according to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (version 25.1 [released September 2022] or the current version). Their severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 5.0 or the current version. Adverse events will be organized by system organ class and preferred term. The vital signs, ECG findings, and physical examination data and change of hematologic and chemistry parameters from baseline will be summarized for each post-baseline visit. Hematologic and chemistry parameters will be categorized as low, normal or high based on laboratory normal ranges and presented as shifts from baseline.

PK samples will be collected at pre-specified time points for noncompartmental data analysis. The PK parameters include but are not limited to: C_{max}, t_{max}, AUC, CL/F, and $t_{½}$.

For determination of the food effect, for selected PK parameters (e.g., C_{max}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$), comparisons between the fed and fasted conditions will be made.

An interim analysis of safety and PK data from Part 1 was conducted to support additional regulatory submissions. A detailed description of data analyses and statistical methods will be outlined separately in the Statistical Analysis Plan.

Date: 12 December 2024

Schedule of Assessments: The SOAs for Part 1 (SAD) and Part 2 (MAD), and Food-effect Cohort are presented in Table 2, Table 3, and Table 4, respectively.

Table 2: Schedule of Assessments: Part 1 (SAD)

Procedure	Screening (Days -28 to -1)	Study Day						
		-1	1	2	3	4	8 ± 1 D	(EOS)[a] 15 ± 2 D
Informed Consent	X							
Eligibility criteria review	X	X						
Demographics[b]	X							
Medical and surgical histories	X	X						
Vital signs[c]	X	X	X	X	X	X	X	X
Physical examination[d]	X	X	X	X	X	X	X	X
Ophthalmologic examination (routine visual acuity and funduscopic examination)	X							X
Pregnancy test[e]	X	X						X
SARS-CoV-2 test[f]		X						
Concomitant medications	X	X	X	X	X	X	X	X
AEs			X	X	X	X	X	X
12-lead ECG	X	X	X[g]			X		X
Hematology[h]	X	X		X		X	X	X
Drug test and alcohol test (urine)	X	X						
Serology[i]	X							
Serum chemistry[h] and coagulation	X	X		X		X	X	X
Urinalysis[h]	X	X					X	X
Admittance to study center		X						
Randomization			X					
PK (plasma)[j]			X	X	X	X	X	X
Study drug administration			X					
Discharge from study center						X		

Abbreviations: AEs = adverse events; D = Day(s); ECG = electrocardiogram; EOS = End of Study; HbsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; min = minute(s); PK = pharmacokinetics.

[a] If the subject withdraws from the study prematurely, the EOS visit is to be conducted within 7 days after the study drug dose.

[b] Includes subject's sex, age, race, and ethnicity, as permitted by local privacy regulations.

[c] Vital signs include systolic (SBP) and diastolic blood pressure (DBP), pulse, respiration rate, and oral temperature (includes height, weight and BMI at the Screening Visit). Vital signs (except for height and weight) will be monitored periodically during and following study drug administration. Subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. The following vital sign collection time points and windows are applicable during the confinement period for the SAD part of the study: Pre-dose (±60 min), 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), 4 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), 24 hr (Day 2) (±30 min), 48 hr (Day 3) (±30 min), and 72 hr (±30 min) (Day 4).

[d] Physical examination will be complete at Screening and symptom-directed for all other study days. At a minimum, the complete physical examination should include general appearance, skin, head, eyes, ears nose and throat (HEENT), mouth/dental (if required), neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, and neurological. A symptom-directed physical examination will include assessment of any new subject complaints or changes from baseline as clinically indicated.

[e] Serum test at Screening, urine test at other time points; for post-menopausal subjects, a blood sample will also be tested for follicle stimulating hormone to confirm post-menopausal status.

[f] SARS-CoV-2 testing should be performed prior to all inpatient stays and may be done at any time during the study based on subject clinical presentation or changes to local pandemic status or health directives.

[g] Triplicate ECGs will be extracted from Holter monitor 120 minutes post-dose (assumed C_{max}) on Day 1 in Cohort 1, with all measurements taken within 5 minutes apart. Subjects should be supine for 10 minutes prior to ECG. Thereafter, in subsequent cohorts, the ECG is to be performed at the time point coincident with C_{max}, as determined in Cohort 1. Continuous 12-lead ECG data will be collected from pre-dose until at least 6 hours post, this data will be collected and stored.

[h] Samples must be collected following a minimum 8 hour fast.

[i] Serology includes HbsAg, anti-HCV Ab, anti-HIV Ab.

[j] PK assessments should be performed on Day 1 predose, and at 15 and 30 minutes, then 1, 2, 4, 6, and 12 hours after dosing, then subsequently on Days 2, 3, 4, 8 and EOS at approximately the same time as the dose of study drug was administered. The PK collection windows are located in Section 6.15.

Table 3: Schedule of Assessments: Part 2 (MAD)

Procedure	Screening (Days -35 to -1)	Study Day[a]										
		-1	1	2	3-7	8	9	10	11	17 ± 2 D	25 ± 2 D	(EOS)[b] 39 ± 2 D
Informed Consent	X											
Eligibility criteria review	X	X										
Demographics[c]	X											
Medical and surgical histories	X	X										
Waist Measurement	X	X			X (D5 only)			X		X		X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic examination (routine visual acuity and funduscopic examination)[r]	X							X				X
Pregnancy test[f]	X	X										X
SARS-CoV-2 test[g]		X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X	X	X	X	X	X	X	X				X
Hematology[i]	X	X		X	X[n]			X		X	X	X
Drug and alcohol test (urine)	X	X										
Serology[j]	X											
Serum chemistry[i]	X	X		X	X	X[p]		X		X	X	X
Coagulation, lipid panel, albumin, globulin[i]	X	X		X	X[n]			X		X		
Insulin[o]		X			X			X				
Urinalysis[i]	X	X		X	X[n]			X		X	X	X
SITZMARKS® Test	X			X[l]	X[m]							

Procedure	Screening (Days -35 to -1)	Study Day[a]										
		-1	1	2	3-7	8	9	10	11	17 ± 2 D	25 ± 2 D	(EOS)[b] 39 ± 2 D
Admittance to study center		X										
Food Consumption Measurement		X	X	X	X	X	X	X				
Randomization			X									
Pharmacokinetics (plasma)[k]			X	X		X		X		X		X
Study drug administration[a]			X	X	X	X	X	X				
Clinical Questionnaire	X[q]	X[q]	X	X	X	X	X	X	X	X	X	X
Serum Tryptase and Plasma Histamine[s]		X	X	X				X		X		
Discharge from study center									X			

Abbreviations: D = Day(s); ECG = electrocardiogram; EOS = End of Study; HbsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; min = minute(s); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a Study drug will be administered approximately 10 hours apart (on any given day) in the clinic on Days 1-10.

b If the subject withdraws from the study prematurely, the EOS visit is to be conducted within 7 days after the last study drug dose.

c Includes subject's sex, age, race, and ethnicity, as permitted by local privacy regulations.

d Vital signs include systolic (SBP) and diastolic blood pressure (DBP), pulse, respiration rate, and oral temperature. At the Screening Visit, height, weight and BMI will be measured. At subsequent visits, the weight and BMI will be measured once per day. Vital signs will be monitored periodically during and following study drug administration. Subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. The following vital sign collection time points and windows are applicable during the confinement period for the MAD part of the study: For the first dose on Day 1: within 60 min pre-dose, 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), 4 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), and 24 hr (can be combined with pre-dose for the following dose day, where applicable) (24 hour/ predose ±30 min). For the second dose on Day 1, within 60 min pre-dose (±10 min), 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), and 4 hr (±10 min). For Days 2-10, vital signs will be measured only one hour post-dose (±10 min) for each dose (e.g., AM and PM doses). On Day 11, Day 17, Day 25, and the EOS visit (or early termination), one exit vital signs measurement will be taken. In addition, orthostatic vitals will be collected on Day-1, Day 2, Day 4, Day 6, Day 8, Day 10, Day 17, Day 25, and Day 39. On Day -1, the Active Stand Test (also known as the NASA 10-Minute Lean Test) will be conducted. To perform the Active Stand Test, subjects should rest supine for 5–10 minutes to establish a baseline heart rate and blood pressure. Once the baseline heart rate and blood pressure are recorded, the subject must stand upright against a wall, with heels placed approximately 2 inches (5 cm) away from the wall, allowing for a slight backward lean. Once the subject is in position, measure heart rate and blood pressure every 2 minutes (+/- 30 seconds) for 10 minutes total. The subject should be instructed to avoid speaking or moving while conducting the Active Stand Test. During the dosing period (Days 1–10), orthostatic vitals will be collected 4 hours (+/- 15 mins) post the morning dose only.

e Complete physical examination will be complete at Screening and symptom-directed for all other study days. At a minimum, the complete physical examination should include general appearance, skin, HEENT, mouth/dental (if required), neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, and neurological. A symptom-directed physical examination will include assessment of any new subject complaints or changes from baseline as clinically indicated.

f Serum test at Screening and urine hCG at other time points; for post-menopausal subjects, a blood sample will also be tested for follicle stimulating hormone at the Screening Visit to confirm post-menopausal status. Once post-menopausal status is confirmed, pregnancy tests will not be required at subsequent timepoints.

g SARS-CoV-2 testing should be performed prior to all inpatient stays and may be done at any time during the study based on subject clinical presentation or changes to local pandemic status or health directives.

h Baseline triplicate ECGs will be extracted from the Holter monitor on Day 1 within one hour prior to the morning dose only.Additionally, triplicate ECGs will be extracted from Holter monitor 6 hour post-dose (for both doses). Triplicate ECG measurements should be taken within 5 minutes apart. Subjects should be supine for 10 minutes prior to ECG. Continuous 12-lead ECG data will be collected from pre-dose until at least 6 hours post-dose for both doses (for Cohorts 9-11); this data will be collected and stored.

i Samples must be collected following a minimum 8 hour fast.

j Serology includes HbsAg, anti-HCV Ab, anti-HIV Ab.

k PK assessments should be performed on Day 1 and Day 10 predose, and at 30 minutes, then 1, 2, 4, 6, 8, 10 (prior to second daily dose), 12, 14, and 24 hours (can be combined with pre-dose for the following dose day, where applicable, 24 hour/ predose ±30 min) after initial morning dose. A pre-dose sample and a sample 6 hours after dosing should be collected on Days 2 and 8 (only for the initial daily dose), and a pre-dose sample should be collected on Day 3. A PK sample should also be collected on Days 17 and 39 (EOS). The PK collection windows are located in Section 6.15.

l Day 2 administration of capsule with radiopaque markers between BID doses of study drug (i.e., approximately 5 hours after the morning dose of study drug on Day 2).

m Day 7 abdominal X-ray to read number of radiopaque markers not expelled.

n On Day 5 only.

o Insulin sampled Day -1, 5, 10. Samples must be collected following a minimum 8 hour fast.

p Blood glucose only

q Screening clinical questionnaire (eligibility and baseline)

r The ophthalmologic examination may be done +/- 1 day. The EOS ophthalmologic examination may be waived if an ophthalmologic examination was completed at Day 10.

s Serum tryptase and plasma histamine tests on Day -1 are not required to assess for subject eligibility. On dosing days (Day 1, Day 2, Day 10 and Day 17), the serum tryptase and plasma histamine tests should be collected after the morning dose only. Serum tryptase should be collected 6 hours (+/- 15 minutes) after the morning dose. When the tryptase sample is drawn, serum should be separated from cells within 3 hours of collection. Within 24 hours prior to sample collection, subjects should not be administered antihistamines, oral corticosteroids, or substances that block H_2 receptors.

Table 4: Schedule of Assessments: Food Effect Cohort(s)

Procedure	Screening (Days -28±7 to -1)	Study Day												
		Period 1						Period 2[a]						
		-1	1	2	3	4	8 ± 1 D	14	15	16	17	18	22 ± 1 D	(EOS)[b] 29 ± 2 D
Informed Consent	X													
Eligibility criteria review	X	X						X						
Demographics[c]	X													
Medical and surgical histories	X	X												
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic examination (routine visual acuity and funduscopic examination)	X							X						X
Pregnancy test[f]	X	X						X						X
SARS-CoV-2 test[g]		X						X						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X[h]			X		X	X[h]			X		X
Hematology[i]	X	X		X		X	X	X		X		X	X	X
Drug and alcohol test (urine)	X	X						X						
Serology[j]	X													
Serum chemistry[i] and coagulation	X	X		X		X	X	X		X		X	X	X
Urinalysis	X	X					X	X					X	X
Admittance to study center		X						X						
Randomization			X											
PK (plasma)[k]			X	X	X	X	X		X	X	X	X	X	X
Study drug administration			X						X					
Discharge from study center						X						X		

Abbreviations: AEs = adverse events; D = Day(s); ECG = electrocardiogram; EOS = End of Study; HbsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; min = minute(s); PK = pharmacokinetics.

[a] The second study drug dose is to be administered in the fasted state at least 14 days after the first study drug dose.

[b] If the subject withdraws from the study prematurely, the EOS visit is to be conducted within 7 days after the study drug dose.
After completion of Period 1, if the initiation of Period 2 is delayed > 1 week (i.e., > Day 14), then the assessments scheduled for the EOS visit are to be completed on Day 15.

[c] Includes subject's sex, age, race, and ethnicity, as permitted by local privacy regulations.

[d] Vital signs include systolic (SBP) and diastolic blood pressure (DBP), pulse, respiration rate, and oral temperature (includes height, weight, and BMI at the Screening Visit). Vital signs (except for height and weight) will be monitored periodically during and following study drug administration. Singular measurements are to be collected. Subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. The following vital sign collection time points and windows are applicable during the confinement period for the Food Effect part of the study: within 60 min pre-dose, 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), 4 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), 24 hr (Day 2 and Day 16) (±30 min), 48 hr (Day 3 and Day 17) (±30 min), 72 hr (±30 min), Day 4 and Day 18 (±30 min).

[e] Physical examination will be *complete* at Screening and *symptom-directed* for all other study days. At a minimum, the *complete physical examination* should include general appearance, skin, head, eyes, ears nose and throat (HEENT), mouth/dental (if required), neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, and neurological. A *symptom-directed physical examination* will include assessment of any new subject complaints or changes from baseline as clinically indicated.

[f] Serum test at Screening and at other time points; for post-menopausal subjects, a blood sample will also be tested for follicle stimulating hormone to confirm post-menopausal status.

[g] SARS-CoV-2 testing should be performed prior to all inpatient stays and may be done at any time during the study based on subject clinical presentation or changes to local pandemic status or health directives.

[h] Triplicate ECGs will be extracted from Holter monitor 120 minutes post-dose (assumed C_{max}) on Day 1 in Cohort 1, with each measurement taken within 5 minutes. Subjects should be supine for 10 minutes prior to ECG. Thereafter, in subsequent cohorts, the ECG is to be performed at the time point coincident with C_{max}, as determined in Cohort 1.

[i] Samples must be collected following a minimum 8 hour fast.

[j] Serology includes HbsAg, anti-HCV Ab, anti-HIV Ab.

[k] PK assessments should be performed 60 min predose and at 15 and 30 minutes, then 1, 2, 4, 6, and 12 hours after dosing, then subsequently 24, 48, 72, and 168 hours after each dose and at the EOS at approximately the same time as the dose of study drug was administered. The PK collection windows are located in Section 6.15.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and specialist terms used in this study protocol are defined in Table 5.

Table 5: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
Ab	antibody
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of Special Interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration time profile
BID	twice daily (*bis in die*)
BMI	body mass index
BUN	blood urea nitrogen
CAPV	Chapare virus
CFR	Code of Federal Regulations
CL/F	apparent clearance
C_{max}	maximum concentration
CYP	cytochrome P450
DBP	diastolic blood pressure
DoD	US Department of Defense
DTRA	Defense Threat Reduction Agency
EC_{50}	50% effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
FIH	first-in-human
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
GP	glycoprotein

Abbreviation or Specialist Term	Definition
GTOV	Guanarito virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HEENT	head, ears, eyes, nose, and throat
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	intravenous
LASV	Lassa virus
LCMV	Lymphocytic Choriomeningitis virus
LHF	Lassa hemorrhagic fever
LUJV	Lujo virus
MACV	Machupo virus
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NASA	National Aeronautics and Space Administration
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
OHRO	Office of Human Research Oversight
OTC	over-the-counter
PK	pharmacokinetic
PO	oral (*per os*)
PT	prothrombin time
PTT	partial thromboplastin time
PXR	pregnane X receptor
QD	once daily (*quaque die*)
QTcF	QT duration corrected for heart rate by Fridericia's formula
RBC	red blood cell
RP2D	recommended Phase 2 dose

Abbreviation or Specialist Term	Definition
SABV	Sabia virus
SAD	single ascending dose
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SOP	standard operating procedure
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TK	toxicokinetic
t_{max}	time of maximum concentration
TPGS	D-α-tocopherol polyethylene glycol 1000 succinate
US	United States
VYR	virus yield reduction
V_z/F	apparent volume of distribution
WBC	white blood cell

1. INTRODUCTION

1.1. Arenaviruses

The Arenaviridae family of viruses is comprised of a large number of Old World (Africa) and New World (Americas) species. Eight of these viruses, including the Old World viruses Lassa (LASV), Lujo (LUJV) and Lymphocytic Choriomeningitis (LCMV) and the New World arenaviruses Junin (JUNV), Machupo (MACV), Guanarito (GTOV), Sabia (SABV) and Chapare (CAPV), are pathological to humans (Hallam 2018; Shao 2015; Brisse 2019); six of which are listed as NIAID Category A priority pathogens (Borio 2002).[1] The most significant unmet medical need associated with these viruses is Lassa hemorrhagic fever (LHF), a potentially fatal human disease associated with LASV infection (Garnett 2019).

LASV is endemic to regions of Western Africa where it is estimated that ~300,000 new LASV infections and ~5000 deaths occur from LHF each year (Balogun 2020). LASV infections are primarily transmitted through inhalation or ingestion of rodent droppings or urine, although it can also spread from human to human via contact with contaminated bodily fluids and excretions. While ~80% of those infected with Lassa virus exhibit mild or no symptoms, the remaining ~20% develop more severe disease following a typical incubation period of 6–21 days (Asogun 2019; Ibekwe 2011; Raabe 2022). The onset of symptomatic disease is usually gradual, starting with fever, general weakness, and malaise whereupon after a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhea, cough, and abdominal pain may follow. In severe cases, facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract may develop along with shock, seizures, tremor, disorientation, low blood pressure and coma. In hospitalized patients, there is a 15-20% mortality rate within 14 days of onset. Given the lack of current vaccine and/or therapeutic treatments options, the development of potent and specific agents to treat LHF and other arenavirus hemorrhagic fevers is urgently needed.

The arenavirus glycoprotein (GP), which is proteolytically processed into the SSP, GP1 and GP2 proteins, assembles to form a stable transmembrane protein complex that is responsible for viral entry and intracellular membrane fusion (Nunberg 2012; Pennington 2022). Arisan identified a novel chemical series that binds to the GP2 subunit and blocks membrane fusion and release of the viral genome intracellularly for replication of new viral progeny. After several iterative rounds of medicinal chemistry and assessment of antiviral activity, absorption, distribution, metabolism, and excretion (ADME) and drug-like properties, ARN-75039 was identified, demonstrating broad-spectrum low nanomolar to sub-nanomolar 50% effective concentration (EC_{50}) activities in VSV-pseudovirus assays expressing GP from both human pathogenic Old and New World arenaviruses including LASV, JUNV, MACV, GTOV and CAPV as well as sub-nanomolar and 1 nM EC_{90} values against replicative LASV and JUNV isolates, respectively in a virus yield reduction assay (Plewe 2021).

[1] NIAD, Biodefense and Emerging Infectious Diseases. NIAID category A, B, and C priority pathogens; July 2022. https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens.

1.2. ARN-75039

ARN-75039 capsules are proposed for the treatment of patients with LASV infection. As an oral suspension (once daily [QD] dosing) ARN-75039 demonstrated a significant reduction of viremia as well as protection against lethal infection in both prophylactic and post-exposure administration rodent models of LHF and two New World arenavirus species (Gowen 2021; Westover 2022). In dogs, ARN-75039 capsules were observed to provide equal to superior pharmacokinetic (PK) exposure to the suspension formulation and will therefore be assessed for safety and tolerability in Phase 1 healthy adult subjects.

1.2.1. In Vitro Efficacy

Results of *in vitro* studies with ARN-75039 demonstrated potent broad-spectrum efficacy against both Old and New World arenavirus glycoprotein VSV pseudotype reporter viruses *in vitro* (Pennington 2022). This inhibitory activity translated to wild-type replicative viruses including LASV, JUNV and Tacaribe virus (TCRV) *in vitro* virus yield reduction (VYR) assays with sub-nanomolar to single nanomolar EC_{90} values, and subsequently further translated to *in vivo* animal models of LASV, JUNV, and TCRV (Gowen 2021; Westover 2022). ARN-75039 is well tolerated with multi-day dosing and it has demonstrated both steady-state plasma and tissue exposure levels > 1000-fold the observed EC_{90} values. The results of these studies establish ARN-75039 as a potent broad-spectrum arenavirus fusion inhibitor and promising new approach for treating severe arenaviral diseases. In addition, no obvious off-target adverse findings have been found based on *in vitro* studies, reducing initial concerns for potential off-target effects associated with ARN-75039 administration.

1.2.2. Single Dose Pharmacokinetics in Nonclinical Species

The single-dose PK of ARN-75039 was evaluated in nonclinical species following intravenous (IV) and oral (PO) administration. ARN-75039 was moderately absorbed after a single oral dose with oral bioavailability observed at 43% in rats and 55% in Beagle dogs with ARN-75039 formulated in Vitamin-E-D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400, glycerin, methylcellulose, sodium citrate buffer and water as an oral suspension.

1.2.3. Toxicology Studies in the Rat and Dog

In exploratory oral toxicology studies with ARN-75039 in the rat, systemic exposures (maximum concentration ([C_{max}] and area under the curve from time 0 to 4 hours [$AUC_{0\text{-}4h}$]) to ARN-75039 increased with increasing doses in a generally less than dose-proportional manner on Day 1 and in a dose-proportional manner on Day 7. Exposure to ARN-75039 was similar between female and male rats. The toxicokinetics (TK) in day 1 animals was lower than expected based on PK studies in male rats at 10 mg/kg where C_{max} and $AUC_{0\text{-}24}$ were 1056 ng/mL and 14347 hr*ng/mL whereas for example the low dose 80 mg/kg/d group of male rats day 1 TK C_{max} and $AUC_{0\text{-}24}$ were 427 ng/mL and 4640 hr*ng/mL, respectively. A repeat single dose PK study at 80 mg/kg in 3 male rats at the same facility that did the 7-day repeat dose exploratory toxicology study reported C_{max} and $AUC_{0\text{-}24}$ of 2400 ng/mL and 49,600 hr*ng/mL, respectively. The Day 1 TK was 6-10 fold lower for the low dose rats and it was also observed that both the mid and high

dose day 1 TK was lower than expected and therefore, the lack of dose proportionality at Day 1 is doubtful especially since the Day 7 TK demonstrated dose proportionality.

In a 7-day repeat dose exploratory toxicology study in the beagle dog, systemic exposures (C_{max}) to ARN-75039 generally decreased with escalating dose on Day 1 and increased in a generally less than dose-proportional manner on Day 7, while total exposure to ARN-75039 (AUC_{last}) increased in a generally less than dose-proportional manner on both Day 1 and Day 7. Sex differences (females>males) were observed in C_{max} and AUC_{last} values following administration of 100 and 300 mg/kg/day ARN-75039 on Day 1 and in AUC_{last} at 300 mg/kg/day on Day 7. However, it is possible that, like in the rat study, the male dogs were underdosed on Day 1 since there was no significant sex difference (fold differences less than 2) on Day 7 at 100, 300 and 1000 mg/kg. Similarly, AUCs were less than 2-fold different between male and female dogs at 100 and 1000 mg/kg. The C_{max} for male dogs on Day 1 at 100 mg/kg was 1740 ng/mL whereas in a separate PK study at a different site, dogs receiving oral doses of 10 mg/kg in the same formulation resulted in a mean C_{max} of 1692 ng/mL.

1.2.4. Plasma Protein Binding Across Species

The extent of ARN-75039 binding to plasma proteins was similar across species with mean unbound fraction (f_u) values of <1% for mouse, rat, guinea pig, dog, and human.

1.2.5. Metabolism Across Species

ARN-75039 had no inhibitory effect (IC_{50} >60 μM) towards cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and CYP3A4 (midazolam substrate). CYP3A4 inhibition for ARN-75039 (testosterone as the subtrate) exhibited an IC_{50} of 20 μM. Reaction phenotyping experiments with ARN-75039 using human recombinant CYPs revealed limited metabolism mediated by CYP3A4, representing approximately 20% metabolism post incubations. ARN-75039 at concentrations up to 10 μM did not activate human pregnane X receptor (PXR) or enhance CYP3A4 mediated metabolism *in vitro*. Metabolism of ARN-75039 using mouse, rat, dog, monkey and human cryopreserved hepatocytes revealed a total of nine putative metabolites (oxidative products and glucuronide conjugates) and demonstrated cross species metabolism. Results from these studies highlight no evidence for human-specific metabolites and support the choice of rats and dogs as metabolically-relevant species for human risk assessment.

1.2.6. Cardiovascular and Functional Observational Battery Assessments in Dogs

Four male beagle dogs, previously implanted with telemetry devices, were administered either vehicle or ARN-75039 (100, 300, and 1000 mg/kg) via oral gavage in a 4×4 Latin square design with a 7-day washout period between dosing occasions. On each dosing occasion (Days 0, 7, 14, and 21), blood pressure, heart rate, ECG, and temperature data were recorded beginning at least 2 hours prior to dose administration and continuing in 5 phases, each consisting or four 60-minute intervals, until approximately 24 hours post-dose. Quantitative and qualitative cardiovascular endpoints evaluated included: heart rate; arterial blood pressure (systolic, diastolic and mean); body temperature; PR interval; RR interval, QRS interval, QT interval; heart-rate corrected QT interval [QTcI (individual-animal correction) and QTcVW (Van der Waters correction)]; and ECG waveform (for ECG morphology and cardiac

arrhythmias). ARN-75039-related increases in mean heart rate were noted at 100 mg/kg (n=4) and 300 mg/kg (n=4). Data collected at 1000 mg/kg (n=2) were excluded from evaluation due to dose-limiting emesis at the first two dosing occasions (Day 0 and Day 7). At 1-4 hours post-dose and at 9-14 hours post-dose, biologically relevant increases in mean heart rate values (up to 36% vs. control at 9-14 hours post-dose) were noted at 100 and 300 mg/kg. At 15-20 hours post-dose, a statistically significant increase in mean heart rate (+38% vs. control) was noted at 300 mg/kg. Biologically relevant (but not statistically significant) corresponding increases in mean RR interval duration were noted at 100 and 300 mg/kg at 9-20 hours post-dose.

These effects on heart rate were accompanied by ARN-75039-related increases in mean heart-rate corrected QT interval duration (QTcVW and QTcI) at 100 mg/kg (n=4) and 300 mg/kg (n=4). Data collected at 1000 mg/kg (n=2) were excluded from evaluation. Biologically relevant (but not statistically significant) increases in mean QTcVW interval duration (up to +9% vs. control at 4 hours post-dose) were noted at the 1-4 and 5-8 hour post-dose intervals at 100 and 300 mg/kg. At the 9-14 hour post-dose interval, the mean QTcVW value was significantly increased (+5% vs. control) at 300 mg/kg. Mean QTcVW values were significantly increased at 100 and 300 mg/kg (up to +4% vs. control) at 15 and 17 hours post dose, respectively. Additionally, biologically relevant (but not statistically significant) increases in mean QTcI interval duration (up to +9% vs. control at 4 hours post-dose) were noted at 100 and 300 mg/kg at the 1-4 hour and 5-8 hour post-dose intervals. At 21-24 hours post-dose, the mean QTcI value at 100 mg/kg remained significantly increased (+4% vs. control). No abnormal ECG waveforms or arrhythmias noted in animals administered 300 mg/kg ARN-75039; ECGs were not evaluated qualitatively at 100 mg/kg due to lack of noteworthy findings at 300 mg/kg. There were no biologically relevant effects of ARN-75039 administration on body temperature at either 100 mg/kg (n=4) or 300 mg/kg (n=4) and there were no biologically relevant effects of ARN-75039 administration on respiratory parameters at either 100 mg/kg (n=4) or 300 mg/kg (n=4).

Functional observational battery parameters were assessed on the first 6 animals/sex/ group prior to initiation of dosing (pre-test) and during the last week of dosing. Assessments included home cage observations, hand-held observations, open field observations and numbers, elicited responses, landing foot splay, grip strength, and body temperature. There were no test article-related effects on any functional observational battery parameters in either sex at any ARN-75039 dose level evaluated.

1.2.7. In Vitro Electrophysiology Studies

A GLP-compliant electrophysiology study (Study 210616.BSS) was conducted to examine the in vitro effects of ARN-75039 on the hERG (human ether-à-go-go-related gene) channel current, a surrogate for IKr, the rapidly activating delayed rectifier cardiac potassium current, at near physiologic temperature. The effects ARN-75039 (0.3, 0.6 and 1 μM) on the hERG potassium channel current were evaluated in whole-cell patch-clamp recordings performed using a manual electrophysiology platform in mammalian (HEK-293) cells that stably express human recombinant hERG mRNA and protein. In this assay, the IC_{50} value for ARN-75039 was 0.46 μM. Under the same experimental conditions, the positive control, 60 nM terfenadine, inhibited hERG current by 77.7%, confirming sensitivity of the test system to hERG inhibition.

An exploratory multiple ion channel assay (Study US034 0009746) was conducted to evaluate the comparative effects of ARN-75039 on potassium (hERG, KCNQ1/mink, Kv4.3/KhIP2 and Kir2.1), sodium (Nav1.5) and calcium (Cav 1.2) ion current was measured using an automated patch clamp platform; current inhibition greater than 50% was considered to represent a significant effect. In this assay, significant ion channel inhibition was limited to the voltage-gated Nav1.5 (Late) sodium ion channel; mean percent current inhibition values for ARN-75039 were 75.71% at 1.67 µM, 90.40% at 5 µM, and 98.65% at 15 µM. The percent current inhibition values for ARN-75039 at all other ion channels, including hERG, were less than 50% at 15 µM.

These data suggest that ARN-75039 would not selectively inhibit hERG/IKr potassium current at free (unbound) plasma concentrations up to 15 µM. On the other hand, results from these screening studies with ARN-75039 indicated biologically meaningful inhibition of Nav1.5 (Late) sodium ion channel current may be expected at free (fu) plasma concentrations at or above the IC_{50} value of 0.55 µM (fu ≥ 0.23 µg/mL). Nav1.5 channels mediate the inward sodium current (INa) and induce fast depolarization, thereby initiating the excitation contraction coupling cascades in the cells. Ina-mediated by Nav1.5 can be classified into peak and late sodium currents (INa-P and INa-L, respectively). The INa-P current is mainly associated with the initiation of cardiac excitability and electrical conduction; INa-P drives the rapid action potential (AP) upstroke, resulting in further channel activation. The INa-L amplitude is much smaller than the INa-P amplitude in many species (approximately 0.1%–1%) and is inactivated more slowly during the plateau of the AP (Veerman 2015). Genetic mutations in SCN5A gene in which some NaV 1.5 channels fail to inactivate, contributing to increased late sodium current (INaL), cause congenital long-QT syndrome type 3 (LQT3) and the risk for arrhythmias (Ruan 2009). Several reports have shown that enhancing Nav1.5 late current can lead to cardiac arrhythmias (Kistamas 2021) and therefore, selectively inhibiting the Nav1.5 late current may have anti-arrhythmic effects (Horváth 2020). Furthermore, blockade Nav1.5-late current has been associated with a reduction in QTc prolongation and Torsades de Pointes even in the presence of hERG block (Belardinelli 2013).

1.2.8. In Vivo Electrocardiographic Effects

ARN-75039 systemic exposures in humans in the range of those achieved in dogs may result in some electrocardiographic changes. While the effects of ARN-75039 on QTc interval duration noted in telemetered dogs were considered test article-related and biologically relevant, the maximum increase in interval duration was nominal (9%), and qualitative ECG analysis revealed no associated waveform abnormalities or arrhythmias. In addition to an association of human Nav1.5 mutations with LQT3 and cardiac arrythmias, Nav1.5 is expressed in GI tissues, and related Nav1.5 mutations are associated with IBS and intestinal motility pathologies (Beyder 2014, Strege 2018, Erickson 2018). Furthermore, oral administration of ranolazine, a selective Nav1.5 late current inhibitor (Fredj 2006), which exhibited an IC_{50} for Nav1.5 late current block of 17 uM vs 0.55 uM for ARN-75039 (Study US034 0009746), has been shown to induce GI-related effects including constipation consistent with reduced intestinal motility (Chandrashekhar 2022, Neshatian 2015).

1.2.9. In Vitro Drug-Drug Interaction Studies

The selectivity of ARN-75039 was evaluated for the potential to interact with other molecular targets across a broad array of 164 targets. In vitro radioligand antagonist binding at a single concentration of 10 µM in duplicate was used to screen 67 targets covering a diverse range of G-protein receptors, neuronal ion channels, and transporters. Targets that demonstrated ≥50% inhibition at 10 µM of ARN-75039 were selected for functional screening. With the exception of the CB_1 receptor where a mixed agonist/antagonist phenotype was observed with an estimated IC_{50} of 3.8 µM and EC_{50} of 7.6 µM. Inhibition of the CB_1 receptor has been associated with significant effects on appetite, emesis and obesity (O'Sullivan 2021, Bosquez-Berger 2023) associated with increased intestinal motility (Vianna 2012, Yeuce 2007) as well as pruritus in mice (Schlosburg 2011, Bilir 2018). The other 17 targets did not demonstrate functional activity up to 10 µM. In a separate study, 97 kinases were screened using a competitive binding assay at a single concentration of 10 µM (Study ARS001-01-p-00001). There was no significant binding to any of the 97 kinases tested. The screening concentrations of 10 µM for off-target activity are approximately 10,000 fold higher, than the EC_{90} determined for BSL-4 wild-type Lassa virus. Thus, an EC_{50} and/or IC_{50} of ≥10 µM represents a reduced risk of inducing undesirable off target activity with ARN-75039, with possible exceptions related to the CB1 receptor, $Na_V1.5$ late current, and the hERG K^+ channel.

The potential for ARN-75039 as a substrate of drug efflux transporter proteins, P-gp and BCRP, was evaluated in Caco-2 cells by measuring bidirectional permeability. BCRP drug efflux was assessed with and without selective transporter inhibitors. From these experiments ARN-75039 was found to be moderately permeable and no efflux. In the presence of the BCRP inhibitor Ko143 (0.5 µM), there was no observed change in efflux ratio. In conclusion, ARN-75039 is not a substrate for either P-gp or BCRP. ARN-75039 was also assessed for transporter substrate potential to other human transporters from kidney and liver including OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, and MATE2K expressed in HEK293. ARN-75039 was not a substrate for any of the additional human transporters tested.

The potential of ARN-75039 to inhibit several known drug transporters was evaluated in HEK293 cells harboring recombinant human transporters, organic anion transporters (OAT1, OAT3), organic anion-transporting polypeptides (OATP1B1, OATP1B3), or organic cation transporter (OCT2), or proton antiporters MATE-2 and MATE-2K (Study 21ARISP-3).

Both P-gp and BCRP were assessed for ARN-75039 inhibition potential in Caco-2 cells. The results from these studies demonstrated that ARN-75039 is not an inhibitor of BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE-2, and MATE-2K. For P-gp, ARN-75039 exerted inhibitory effect with an IC_{50} of 3.54 µM.

Overall, ARN-75039 has a low probability as a victim or perpetrator of most transporters, with the exception of P-gp. Following oral administration, there is a potential for drug interactions with oral drugs known to be substrates of P-gp although because protein binding of ARN-75039 is >99% the probability of inhibiting P-gp is low at clinically relevant dose levels of ARN-75039.

1.2.10. Repeat Dose Toxicity Studies in Rat and Dog

To support the current clinical study, 28-day definitive toxicity studies, with supporting dose range-finding studies were conducted in both rats and dogs using the clinically-relevant route (oral) and schedule (daily) of administration. The primary objective of the definitive studies was to identify no observed adverse effect level (NOAEL) in both species. Definitive studies nonclinical toxicology studies in the rat and dog were conducted in compliance with United States (US) Food and Drug Administration (FDA) Good Laboratory Practice (GLP) regulations. In repeat-dose oral toxicity studies conducted with ARN-75039 in dogs, the 14 day NOAEL was 30 mg/kg/day. In rats, the 17 day (females) / 16 day (males) NOAEL was 50 mg/kg/day and the 28 day NOAEL was 30 mg/kg/day. Based on these NOAEL values, a maximum recommended starting dose (MRSD) of 28.8 (rounded to 30) mg per day was calculated for the current study. Target organs histopathologically identified in ARN-75039-treated animals include the bone marrow (rats and dogs), liver (rats), spleen (rats), stomach (rats) and thymus (dogs). As ARN-75039 is an anti-viral with no intended mammalian molecular target, none of the target organ effects noted in ARN-75039-treated animals were considered to be mechanism-related; all target organ effects were considered to be scaffold-related. The results of standard genotoxicity and phototoxicity studies indicate that ARN-75039 does not pose a genotoxic risk but does pose a potential phototoxic risk to humans.

In the animal studies, however, gastrointestinal (GI)-related effects that included reduced food consumption, vomiting, loss of appetite and body weight were observed in dogs (≥100 mg/kg/day) and rats (100 mg/kg/day). None of these observed changes were confirmed by histological changes.

Note: During Part 1 (SAD) of this study, a low number of drug-related GI associated adverse events (nausea in 3 subjects [37.5%], vomiting in 2 subjects [25.0%], abdominal pain in 1 subject [12.5%], all mild in severity) were observed at the highest dose (2000 mg).

Refer to the ARN-75039 Investigator's Brochure for additional information.

1.2.11. First-in-Human Study

The current clinical study represents the first-in-human (FIH) study of ARN-75039 and is designed as a Phase 1, randomized, double-blind, placebo-controlled, two-part SAD and MAD study in adult healthy adult subjects, with the objective of assessing the safety, tolerability, and PK of ARN-75039 capsules. The effect of food on the PK of ARN-75039 also may be studied.

Note: Part 1 (SAD) of this study has been completed.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
• To assess the safety and tolerability of single and multiple doses of ARN-75039 when administered by the oral route at escalating dose levels in healthy adult subjects.	• Type and frequency of treatment-emergent adverse events (TEAEs). • Type and frequency of treatment-emergent serious adverse events (TESAEs). • Type and frequency of study drug-related Grade > 1 TEAEs. • Type and frequency of changes in clinical laboratory values, electrocardiograms (ECGs), colonic transit time (biomarker), physical examinations, and vital signs.
Secondary Objectives	**Secondary Endpoints**
• To determine the recommended Phase 2 dose (RP2D) and regimen of ARN-75039 capsules.	• RP2D and regimen of ARN-75039 capsules.
• To assess the PK of single and multiple doses of ARN-75039 when administered by the oral route. • To assess the effect of food on the PK of a single oral administrations ARN75039.	• PK parameters of ARN-75039 capsules, including but not limited to: o Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{0-t}). o Appropriate partial AUCs: Area under the concentration-time curve from time 0 to the end of dosing interval (AUC_{0-tau}) or alternative partial AUCs as appropriate to the dosing regimen (eg, AUC_{0-10} for BID, if applicable, and AUC_{0-24} for QD) to properly address the study objectives o Area under plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$). o Maximum observed plasma concentration (C_{max}). o Time to reach C_{max} (t_{max}). o Half-life ($t_{1/2}$). o Apparent clearance after extravascular administration (CL/F). o Apparent volume of distribution during the terminal phase after extravascular administration (V_z/F).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

ARN-75039-101 is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and PK of escalating single and multiple doses of ARN-75039 when administered by the oral route in healthy adult subjects. Pharmacokinetic analysis of hydroxypropyl methylcellulose (HPMC) capsules filled with neat ARN-75039 (10 mg) was assessed in dogs under both fed and fasted conditions. Mean maximum plasma exposures (C_{max}) and AUC_{0-24} were 5.2- and 8.8-fold higher in fed dogs versus fasted dogs. Therefore, it was decided to dose volunteers under fed state conditions. Within each cohort, the first 2 subjects will be randomized 1:1 to receive ARN-75039 capsules or placebo. After a review of the first 3 days of blinded safety (following completion of the Sitzmark® test) for these subjects by the Medical Monitor, an additional 6 subjects will be randomized in a 5:1 (active: placebo) ratio. Following completion of dosing in the SAD part of the study, a planned interim analysis was performed to help determine dose levels in the MAD part of the study. A description of the study cohorts including the study part, dose, number of subjects, and status is presented below in Table 6.

Table 6: Dose Levels and Numbers of Subjects by Cohort

Study Part	Cohort	Meal	Dose	ARN-75039 (Number of Subjects)	Matching Placebo (Number of Subjects)	Status
1: SAD	1	Fed	30 mg	6	2	Completed
	2	Fed	100 mg	6	2	Completed
	3	Fed/Fasted	300 mg (fasted cohort added)	8	2	Completed
	4	Fed	600 mg	6	2	Completed
	5	Fed	1200 mg	6	2	Completed
	6	Fed	2000 mg (up to 2400 mg planned)	6	2	Completed
2: MAD	7	Fed	Day 1: 36 and 24 mg doses Day 2: 24 mg BID Days 3–10: 12 mg BID	6	2	Completed
	8	Fed	Day 1: 75 and 50 mg doses Day 2: 50 mg BID Days 3–10: 25 mg BID	6	2	Completed
	9	Fed	Day 1: 150 and 100 mg doses Day 2: 100 mg BID Days 3–10: 50 mg BID	6	2	Completed
	10	Fed	Day 1: 240 and 160 mg doses Day 2: 160 mg BID Days 3–10: 80 mg BID	6	2	Completed

Study Part	Cohort	Meal	Dose	ARN-75039 (Number of Subjects)	Matching Placebo (Number of Subjects)	Status
	11	Fed	Day 1: 360 and 240 mg doses Day 2: 240 mg BID Days 3–10: 120 mg BID	6	2	Planned

Abbreviations: BID = twice daily (*bis in die*); MAD = multiple ascending dose; SAD = single ascending dose.
Note: BID doses will be administered approximately 10 hours apart.

In Part 2 (MAD), dose regimens include twice daily (BID) dosing and have been designed generally as follows: On Day 1 an initial 3× (relative to maintenance dose) loading dose will be administered followed by a 2× dose. On Day 2, 2× (relative to maintenance dose) BID dosing will be administered. On Days 3–10, BID administration of a 1× maintenance dose will be provided. The dose regimens in Cohorts 7–10 (completed) and Cohort 11 (planned) are provided in the table above. Doses will be administered approximately 10 hours apart. The dose levels and dosing intervals in the MAD cohorts have been determined based on the safety and PK of ARN-75039 demonstrated in the SAD part of the study along with non-clinical general toxicity findings observed in rats and dogs, with the objective of determining the RP2D.

An overview of the conduct of each study part follows:

- **Part 1 SAD:** The SAD part of the study is the FIH study of ARN-75039. Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following a 3-day safety observation period with the approval of the Medical Monitor. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through study Day 8.

  A cohort of subjects in the SAD portion of the study may be enrolled to receive a second dose of study drug in the fasted state following an appropriate washout period, with each dose separated by at least 15 days, in order to assess food effect (including relative bioavailability); the dose level utilized for the food effect cohort(s) will be selected based on the demonstration of adequate safety at the next higher dose level, as assessed by the Safety Monitoring Committee (SMC). The dose level utilized for the food effect cohort(s) will be selected by the SMC based on review of safety data from completed SAD, and as applicable, MAD, cohorts.

  Note: Part 1 has been completed.

- **Part 2 MAD:** The MAD part of the study will be initiated after the safety and PK data from the SAD part of the study have been reviewed by the Food and Drug Administration (FDA) and the Sponsor and FDA have determined that it is safe to proceed. The MAD part of the study will utilize BID oral doses of ARN-75039 for a total of 10 days for each subject, with doses administered approximately 10 hours apart. The proposed doses and dose regimen have been determined based on the safety and PK results from the SAD part of the study and safety margins (ranging from 50- to 8-fold) of predicted $AUC_{0\text{-}24}$ for the proposed dose regimen and mean (both sexes) $AUC_{0\text{-}24}$ of the rat NOAEL at 50 mg/kg.

Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following an 8-day safety observation period during continuous oral dosing. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through Day 8. Up to 5 MAD cohorts are planned , comprising a maximum total of approximately 40 subjects to be treated in Part 2 of the study (30 ARN-75039 and 10 placebo). Additional subjects may be enrolled to compensate for early terminations or per the discretion of the Sponsor

For both the SAD and MAD portions of the study, the occurrence of at least 2 study drug-related Grade > 1 TEAEs in subjects receiving ARN-75039 in any dose cohort will result in convening the SMC to determine whether dosing should be continued or terminated at that dose.

Written informed consent for study participation will be obtained before any study-related procedures or assessments are performed. All potential subjects will be screened for potential participation, and those meeting all eligibility criteria will be offered participation in the study.

Subject participation in the study will be conducted in the following 3 defined periods:

- **Screening Period:** The Screening Period begins when the informed consent form (ICF) is signed. During this period, subjects will undergo baseline assessments to determine eligibility for study participation. The Screening Period duration will be up to 35 days; it will end after all evaluations required to meet eligibility have been completed. If a subject meets all eligibility criteria, they will be offered enrollment into the study.
- **Treatment Period:** The Treatment Period will begin on Day 1 with randomization and administration of the first dose of study drug (ARN-75039 or placebo). The Treatment Period has a duration of 1 day for the SAD part of the study and 10 days for the MAD part of the study.

  During the Treatment Period, 1 dose of study drug will be administered in the SAD part of the study; the number of doses and dosing schedule in the MAD part of the study are summarized in Table 6. The last MAD dose will be administered on Day 10.

  In the food effect cohort(s), subjects will receive the first study drug dose on Day 1 followed by a second dose on Day 15 or thereafter, with the first administered under fed conditions and the second administered under fasted conditions.

  Subjects will have periods of residency at the study site in each part of the study; residency during the SAD part will occur from Day -1 to Day 4 following first study drug dose and residency during the MAD part will occur from Day -1 to Day 11 (approximately 24 hours following the final study drug dose). (Subjects will be discharged after collection of the 24-hour post-dose PK sample.) In the food effect cohort(s), residency will occur from Day -1 to 4 around each study drug dose administration.

  Subjects will return to the study site for follow-up evaluations according to the Schedule of Assessments (SOA) during the Treatment Period (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort).

After completing the Treatment Period, subjects will enter the Safety Follow-up Period.

- **Safety Follow-up Period:** The Safety Follow-up Period will have a duration of 14 days for the SAD part of the study and 28 days for the MAD part of the study, culminating with an End-of-study (EOS) visit. For subjects who withdraw from the study prematurely, the EOS visit is to be conducted within 7 days after the last study drug dose.

Safety will be assessed at each study visit, and assessments of PK will be assessed at specific time points.

Subjects who receive ≥ 1 dose of study drug will be encouraged to complete all study visits. If subjects do not complete all study visits, or terminate early from the study, they will be asked to return to the study site to complete the EOS Visit within 7 days after withdrawal from the study. If a subject is terminated early from the study during their residency at the study site, it is recommended that the EOS Visit be completed on the same day.

If a subject has a study drug-related Grade > 1 TEAE during the Treatment Period, study drug dosing will be discontinued for that subject. These subjects will not be replaced. If a subject has a study drug-related Grade 1 TEAE during the Treatment Period, study drug dosing may be discontinued for that subject per the Investigator's discretion. These subjects may be replaced per the Sponsor's discretion. Subjects discontinued due to TEAEs will be asked to remain in the study and complete the study visits through the EOS visit for safety follow up purposes. If a subject terminates early for a reason unrelated to study participation, the subject may be replaced.

Study drug dose level modifications or dosing administration deviations outside the protocol-specified windows are not permitted during the Treatment Period.

3.2. Safety Monitoring Committee

3.2.1. Sentinel Subject Data Review

Following completion of the two sentinel subjects in each cohort through Day 3 (for the SAD part) or Day 8 (for the MAD part), the Medical Monitor will review the safety data to determine whether the remaining subjects in each cohort may be enrolled into the study.

3.2.2. Dose Escalation Data Review

Following completion of each cohort through Day 8, the SMC will review the safety data in order to determine how to proceed with the study and to select the dose level for the subsequent dose cohort. PK data may be available for consideration but are not required for the SMC meeting for each dose cohort.

The SMC will periodically review all available clinical, GI transit and laboratory data during the study. The SMC will convene and make recommendations regarding cohort advancement and study continuation, discontinuation, or modification.

3.3. Justification for the Study Design

Single and multiple ascending dose designs are commonly used in FIH studies to assess preliminary safety, tolerability, and PK of a study drug in humans. Ascending doses of ARN-75039 were administered in order to evaluate the safety and establish the maximum tolerated dose of ARN-75039 at single doses of 30 to up to 2000 mg and at multiple doses within the range selected based on the findings from the SAD part of the study.

Safety data will be evaluated within and between each cohort. Interim safety reviews will be performed to determine if dosing within a cohort can proceed and if dose-escalation between cohorts can proceed as planned, if the dose planned for the next cohort should be modified, and/or if termination of the clinical study is necessary. Interim reviews of safety and tolerability data help ensure subject safety.

To further ensure the safety of subjects, sentinel dosing will be employed.

This study employs a randomized and double-blind design to minimize bias. A placebo group is included to facilitate identification of effects related to administration of drug rather than the study procedures or situations.

This clinical study is being performed in healthy subjects to avoid interference with the results from disease processes and other drugs. Medications, substances, and food products that may interfere with the assessment of the PK profile of ARN-75039 are prohibited during study participation.

3.4. Number of Subjects

The total number of subjects enrolled in the study is dependent on the number of dose level(s) investigated. In Part 1 (SAD) study, 5 cohorts of 8 subjects are planned (40 adult subjects: 30 ARN-75039 and 10 placebo) with an additional optional cohort (up to 8 additional adult subjects). In the Part 2 (MAD) study, 5 cohorts of 8 subjects (40 subjects: 30 ARN-75039 and 10 placebo) are planneds. Additional subjects may be enrolled to compensate for early terminations or per the discretion of the Sponsor.

3.5. Study Completion

The site will complete the Study Termination page of the electronic case report form (eCRF) which will mark the completion of the subject's participation in the study.

The date of termination is the date of the last contact in which the subject's health status was assessed, or in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the Study Termination eCRF page.

3.6. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Failure of the Investigator to enter subjects at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.
- Regulatory authority request.

Should the study be closed prematurely, all study materials (study drug, etc.) must be returned to the Sponsor or designee (or disposed of as directed by the Sponsor or designee).

4. SELECTION AND WITHDRAWAL OF SUBJECTS

This study will enroll health male and female subjects aged ≥18 and ≤55 years at Screening.

Subjects will be required to meet all of the inclusion criteria and none of the exclusion criteria in order to be eligible for study enrollment; the Sponsor will attempt to reach an overall preferred combined target enrollment goal of ≥30% African American and/or West African adult subjects in order to help assess potential population differences in safety, tolerability and PK in the primary clinical population.

Subject re-screening is allowed for this protocol. In the event that a subject's screening laboratory value is outside the acceptable range, the laboratory test can be repeated once, and if the repeat value is within the acceptable range, the subject can be considered eligible for the study. In the event that a subject fails to meet the overall screening criteria, the subject may repeat the overall screening process once, and if the subject then meets all eligibility criteria, the subject will be considered eligible to enter the study.

4.1. Subject Inclusion Criteria

Subjects meeting all the following criteria are eligible for study participation:

1. Is male or female, age 18 to 55 years, inclusive, at Screening.
2. Body mass index (BMI) between 18.5 and 35 kg/m^2, inclusive, at Screening.
3. In good general health, determined by no clinically significant findings in the opinion of the Investigator from medical history, physical examination, 12-lead ECG, clinical laboratory findings, and vital signs at Screening and Day -1 or 1.
4. Hemoglobin, hematocrit, white blood cell count, absolute neutrophil count, and platelet count results within the laboratory reference range at Screening or without clinically significant abnormalities in the opinion of the Investigator; subjects with Gilbert's disease with associated abnormalities of liver function tests are eligible for enrollment. Tests may be repeated at the discretion of the Investigator to confirm abnormalities.
5. Estimated glomerular filtration rate (eGFR) based on the CKD-EPI equation of ≥ 80 mL/min/1.73 m^2 at Screening
6. Females of childbearing potential must practice effective contraception per national regulatory guidelines for clinical trials from Screening, throughout the study and for 28 days after the EOS visit.
7. Females of childbearing potential must have a negative pregnancy test at Screening and within 24 hours prior to dosing of study drug; for post-menopausal subjects, a blood sample will also be tested for follicle stimulating hormone (FSH) to confirm post-menopausal status (as verified by an FSH of ≥40). Surgically sterile females are eligible; however, proof via medical records will be required.
8. Males must agree to not donate sperm and/or to use condoms during sexual intercourse from the time of the first study drug administration and for 90 days following the last

dose of study drug, and females must agree not to donate eggs from the time of the first study drug administration and for 60 days following the last dose of study drug.

9. Must be willing and able to comply with measures to avoid photosensitivity reactions (i.e., avoidance of outdoor sun exposure and tanning; consistent use of long sleeve shirts, long pants, hats, and sunglasses; consistent use of SPF 75 or greater sunscreen when outdoors) from Day 1 through Day 8 in Part 1 and through Day 25 in Part 2.
10. Able to provide informed consent.
11. Willing and able to comply with this protocol and be available for the entire duration of the study.

4.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Any clinically significant underlying illness in the opinion of the Investigator.
2. Poor venous access.
3. Inability to ingest all capsules of a multi-capsule dose within 5 minutes of ingestion of the first capsule.
4. Prior exposure to ARN-75039.
5. Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening; subjects with adequately treated HCV are eligible for enrollment.
6. Positive test for SARS-CoV-2 infection on Day -1.
7. Consumption of Seville oranges, grapefruit or grapefruit juice within 72 hours prior to Day 1 or during the study.
8. History of drug or alcohol abuse within 1 year of Screening in the opinion of the investigator, or a positive test for drugs of abuse or alcohol at Screening or Day -1.
9. Use of any prescription or over-the-counter (OTC) medications, including food supplements, vitamins, herbal medications (e.g., St. John’s wort), and cannabis, with the exception of contraceptive medications and as needed (prn) acetaminophen or paracetamol (not exceeding 2 grams/day) within 7 days prior to study drug administration and throughout the study.
10. History of malignancy, except adequately treated basal cell carcinoma or in situ carcinoma of the uterine cervix.
11. Smoking greater than 20 cigarettes, cigars, cigarillos or E-cigarettes per week in the 3 months prior to study drug administration or during the study.
12. Any female who is pregnant or breastfeeding, or any female who is planning to become pregnant during the study and safety follow-up period.

13. Any reason or condition that, in the Investigator's opinion, may compromise study participation, present a safety risk to the subject, or may confound the interpretation of the study results.
14. A QT duration corrected for heart rate by Fridericia's formula (QTcF) > 450 millisecond (msec) based on either single or averaged QTcF values of triplicate ECGs obtained over a 3-minute interval (at Screening).
15. Blood product donation within 30 days before Screening.
16. Unwilling to consume breakfast and dinner on study drug administration days.
17. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives of the prior investigational agent (whichever is longer) have passed since ending another investigational device or drug study or plans to enroll in another investigational device or drug study during the course of this study.

Part 2 (MAD) only:

18. History of:
    a. Structural abnormality of the gastrointestinal (GI) tract or a disease or history of a condition that can affect GI motility
    b. Inflammatory bowel disease (even if treated and currently in remission)
    c. Diverticulitis or any other chronic condition such as chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, lactose intolerance that can be associated with abdominal pain or discomfort and could confound the assessments in this trial.
    d. Chronic idiopathic diarrhea
    e. Formally diagnosed colonic inertia or conditions that can be associated with constipation: pseudo-obstruction, colonic inertia, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis. lower tract evacuation disorders, functional outlet delay (e.g., rectal prolapse, anismus, etc.)
19. Current active peptic ulcer disease (i.e., disease that is not adequately treated or stable with therapy.)
20. Potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis.)
21. Subject currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia or any unexplained anemia, or weight loss) or systemic signs of infection or colitis.
22. Subjects who do not expel at least 80% (19 or more) of the markers after the Sitzmarks® colonic transit test administered during the screening period.
23. History of chronic/generalized pruritus and/or skin rash of unknown origin.

24. Subjects with diagnosed Type 1 or Type 2 diabetes, or with a blood glucose value > 125 mg/dL during the screening period.

4.3. Subject Withdrawal Criteria

Study drug dosing will be permanently discontinued in a subject if any of the following occurs:

- Subject experiences any study drug-related Grade > 1 TEAE.
- Subject experiences any study drug-related Grade > 1 adverse event of special interest (AESI) as per Section 6.17.6.
- Subject withdraws consent.
- Subject becomes pregnant.
- Subject is unable to comply with the protocol requirements.
- Sponsor terminates the study.
- Study dosing cessation is mandated by a regulatory authority.

5. TREATMENT OF SUBJECTS

5.1. Description of Study Drug

5.1.1. Study Drug

ARN-75039 will be supplied to the clinical site as neat drug substance. During study conduct, the onsite pharmacist will dispense the specified dose and will encapsulate it in a hydroxypropyl methylcellulose (HPMC) capsule prior to dosing. ARN-75039 capsules are administered orally.

5.1.2. Placebo

During study conduct, the onsite pharmacist will dispense the appropriate amount of microcrystalline cellulose (placebo substance) and will encapsulate it in an HPMC capsule prior to dosing. Placebo capsules are administered orally.

5.2. Treatments Administered

Subjects assigned to active treatment at the time of randomization will receive the investigational product, ARN-75039 capsule(s); subjects assigned to the control group will receive matching placebo capsule(s).

5.3. Selection and Timing of Dose for Each Subject

Study drug is to be administered in the fed state, with subjects served a meal 30 minutes prior to the scheduled study drug dose. Study drug will be administered with 240 mL or the smallest amount of water needed to swallow all the capsules.

If the food effect of ARN-75039 is explored, the second dose will be administered to subjects in this cohort on Day 15 or thereafter; study drug dose will be administered at the study site after an overnight fast of at least 10 hours. Water will be allowed for up to 2 hours prior to dosing, then restricted until 2 hours post-dose, with the exception of water taken (up to 240 mL) with capsule administration.

The number of doses and dosing schedule in the MAD part of the study will be determined based on the safety and available PK data for ARN-75039 demonstrated in the SAD part of the study. The last MAD dose will be administered on Day 10.

5.4. Methods of Assigning Subjects to Treatment Groups

In Part 1 (SAD), subjects will be randomly assigned to receive active ARN-75039 (6 subjects) or matching placebo (2 subjects) in each cohort.

As this is the first in human study of ARN-75039, sentinel dosing will be employed.
Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following a 3-day safety observation period, with the approval of the Medical Monitor. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through Day 9 (see Section 5.5).

In Part 2 (MAD), subjects will be randomly assigned to receive active ARN-75039 (6 subjects) or matching placebo (2 subjects) in each cohort. Two sentinel subjects per cohort will be randomized (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed following an 8-day safety observation period during continuous oral dosing, with the approval of the Medical Monitor. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through Day 8 (see Section 5.5).

5.5. Individual, Dose Escalation, and Study Stopping Rules

5.5.1. Definition of Recommended Phase 2 Dose

The RP2D is defined as the ARN-75039 dose demonstrating an appropriate safety, PK, and benefit/risk profile to advance into late phase development.

5.5.2. Individual Stopping Rules

Dosing of ARN-75039 will be permanently discontinued in a subject if any of the following occurs:

- Subject experiences any study drug-related Grade > 1 TEAE
- Subject experiences any study drug-related Grade > 1 adverse event of special interest (AESI)
- Subject withdraws consent
- Subject becomes pregnant
- Subject is unable to comply with the protocol requirements
- Sponsor terminates the study
- Study dosing cessation is mandated by a regulatory authority

5.5.3. Dose Escalation Stopping Rules

Dose escalation stopping rules will be used to determine whether or not investigation of a higher dose level will proceed per protocol. If 2 or more subjects receiving ARN-75039 experience a study drug-related Grade > 1 TEAE in a single cohort, further enrollment to the respective dose cohort will be stopped, and all study drug administration may be suspended, pending SMC evaluation of all available safety and PK data. After its evaluation, the SMC may recommend study continuation (with or without modification) or termination of dose escalation; the SMC may also recommend de-escalation to lower doses. If dose escalation is terminated for safety reasons, the next-lower dose may be declared the highest tolerable dose. Alternatively, an additional cohort at an intermediate dose may be added to better define the highest tolerable dose. The SMC will also evaluate the PK profile of ARN-75039 when administered by the oral route to determine if a threshold exposure associated with potential anti-viral activity has been achieved which might correspond to the RP2D.

5.5.4. Study Stopping Rules

The study may be stopped at the discretion of the sponsor based on recommendations of the SMC, or for any reason specified in Section 3.6 Criteria for Study Termination. In all cases, all necessary measures will be taken to ensure appropriate safety follow-up of all subjects in the trial.

5.6. Blinding

This study employs a randomized, placebo-controlled, double-blind, dose-escalation study design to determine the safety, tolerability, and PK of single and repeat doses of ARN-75039, respectively. ARN-75039 drug substance will be provided. The onsite pharmacist or designee will calculate and encapsulate the ARN-75039 dose and distribute the appropriate dose based on the randomization scheme.

For all dosing cohorts, the subjects, Investigator, and Sponsor will be blinded to the treatment administered until enrollment is complete and the study database is locked, provided there are no safety concerns. In the event of a safety concern, only the blind for the subject(s) who experienced the event(s) of concern will be broken to determine which treatment had been administered (ARN-75039 or placebo). This information will be used to determine whether or not the study will proceed to the next higher dose.

In the event of an emergency, the Investigator can contact the Medical Monitor. If it is determined that unblinding is necessary in order to treat the emergency, after consulting the Medical Monitor/Sponsor, if possible, the Investigator may be unblinded according to the study center's standard operating procedures.

5.7. Concomitant Medications

5.7.1. Prohibited Medications

The following concomitant therapies are prohibited:

- Use of any prescription or OTC medications, including glucagon-like peptide-1 (GLP-1) agonists (e.g., prescribed for weight management), food supplements, vitamins, herbal medications (e.g., St. John's wort), and cannabis, with the exception of contraceptive medications and as needed (prn) acetaminophen or paracetamol (not exceeding 2 grams/day) within 7 days prior to study drug administration and through the EOS visit.
- Any investigational drug or device within 30 days or 5 half-lives of the drug, whichever is the longer, prior to Day 1 and through the EOS.

If deemed necessary by the Investigator, medications for TEAEs may be administered regardless of relationship to treatment with study drug. All concomitant medications taken in conjunction with a TEAE will be recorded in the source documents and in the eCRF.

5.7.2. Contraception

Individuals of reproductive potential who are (hetero) sexually active must be willing to use effective contraception from Screening through 28 days after the EOS visit. (Individuals who are

at least 1 year post-menopausal are not of reproductive potential.) Acceptable means of contraception include:

- Individuals who have been surgically sterilized.
- Females of reproductive potential: diaphragm, injectable, oral/patch contraceptives for a minimum of 6 weeks, contraceptive sponge, implant, or intrauterine device in use prior to enrollment, with use of condom for their male partners.
- Males: condom in combination with any of the above means of contraception for their female partners.
- All individuals: abstinence may be an acceptable means of contraception as long as the individual consents to initiate immediate use of double barrier protection for the duration of the study should (hetero) sexual intercourse occur.

5.7.3. Restrictions

Subjects must adhere to the following restrictions during study participation:

- Use of >20 cigarettes, cigars, cigarillos, or E-cigarettes per week is prohibited within the 3 months prior to Day 1 through the EOS visit.
- No alcohol containing foods or beverages; grapefruit-containing foods or beverages; or Seville orange or orange-containing foods or beverage from within 72 hours before the first study drug dose through the EOS visit.
- No strenuous activity from 48 hours prior to Day -1 through the last PK sample collection time point.
- No blood product donation within 30 days before Screening through the last PK sample collection time point.
- Avoidance of outdoor sun exposure and tanning by consistent use of long sleeve shirts, long pants, hats, and sunglasses and consistent use of SPF 75 or greater sunscreen when outdoors from Day 1 through Day 8 in Part 1 and through Day 25 in Part 2.

5.8. Treatment Compliance

Study drug will be administered orally under the supervision of the Investigator or qualified designee. Since study drug will be orally administered, each subject's buccal cavity will be inspected following dosing to ensure consumption of the encapsulated study drug. In terms of compliance, the study center is required to adhere to all applicable laws, regulations and guidelines including, but not limited to, the US Code of Federal Regulations, the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Health Insurance Portability and Accountability Act of 1996, as well as any applicable local and federal regulations.

5.9. Packaging and Labeling

Study drug will be packaged and labeled in accordance with applicable regulatory requirements. Study drug labels will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being

investigated. As ARN-75039 will be supplied to the clinical site as neat drug substance, the shipment, packaging, and encapsulation of neat drug substance, and the blinded labeling of study drug prior to administration to subjects are detailed in the Pharmacy Manual.

5.10. Investigational Product Retention at Study Site

It is the responsibility of the Investigator to ensure that all neat drug substance received at the clinical pharmacology unit is inventoried and accounted for by the recording of details pertaining to study drug in an accountability log provided, or otherwise approved by the Sponsor. Study drug accountability will be verified during on-site monitoring visits.

At the end of the study, the study monitor will conduct a final accountability of all neat drug substance and/or encapsulated study drug. The Sponsor will make a determination at the end of the study if the remaining drug substance is to be destroyed at the site, per the pharmacy's standard operating procedures (SOPs) or shipped to a suitable location specified by the Sponsor.

6. STUDY PROCEDURES

6.1. Informed Consent

Each subject must sign and date the ICF before participating in any study-specific activities. The ICF may be signed prior to the Screening Visit. After the ICF is signed, the subject enters the Screening Period.

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

A complete description of the study is to be presented to each potential subject and signed and dated informed consent is to be obtained before any study specific procedures are performed.

6.2. Medical History

A complete medical and surgical history along with demographic data will be obtained for all subjects during Screening. Data to be recorded in the source document and eCRF include the subject's sex, race, date of birth, and concomitant medication use.

A recent medical history will be obtained upon admittance to the clinic and prior to study drug dosing to assess continued study eligibility and adherence to final inclusion/exclusion criteria. This recent medical history includes a review for changes from Screening as well as a review of the subject's recent medication use.

In Part 2 (MAD), subjects will be administered a specially-designed clinical questionnaire according to the frequency outlined in Table 3.

- The clinical questionnaire will capture data relating to the following symptoms:
    - Nausea
    - Vomiting
    - Abdominal pain: generalized/localized/distention/cramp-like/colicky (according to from modified Rome IV® criteria)
    - History of diarrhea or constipation (at baseline only)
    - Frequency and stool consistency of bowel movements since start of study drug dosing (e.g., decreased/increased constipation/diarrhea/colitis)
    - Anxiety and depression symptoms

6.3. Physical Examination

A complete physical examination will be conducted at the time points designated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort). At other designated time points, a partial (symptom-directed) physical examination may be conducted.

- At a minimum, the complete physical examination should include general appearance, skin, HEENT (head, eyes, ears, nose, and throat), neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, and neurological.
- A symptom-directed physical examination will include assessment of any new subject complaints or changes from baseline as clinically indicated.

Changes from baseline in any physical examination findings identified by the Investigator as clinically significant must be recorded as an AE on the appropriate eCRF.

6.4. Electrocardiograms

ECGs will be extracted from the Holter monitor (in triplicate, with all measurement within 5 minutes apart) at the time points indicated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort). Subjects should be supine for 10 minutes prior to ECG. The date and time of each ECG and its results will be documented in the source documents and transcribed into the eCRF. Continuous 12-lead ECG data will be collected from pre-dose until at least 6 hours post (for both doses in the MAD portion of the study); this data will be collected and stored.

6.5. Alcohol and Drug Screening

Subjects will undergo urine drug and alcohol screening to confirm the absence of alcohol or substances of abuse (including amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids) at Screening, on Day -1, and at any time during the study as warranted by the Investigator or study staff. In accordance with the exclusion criteria (Section 4.2) any individual who has a test reflecting recent use of alcohol or illicit substances prior to the first study drug dose must not be enrolled in the study. Analytes for the urine drug test are specified in Table 7.

6.6. Screening Serology

A blood sample for screening serology, including measurement of hepatitis B surface antigen (HbsAg), anti-HCV antibody (Ab), and anti-HIV Ab, is to be collected during Screening. Results must be negative for the subject to be eligible for the study; however, subjects with adequately treated HCV (HCV ribonucleic acid negative) are eligible for enrollment.

6.7. SARS-CoV-2 Testing

Rapid antigen or polymerase chain reaction testing for SARS-CoV-2 via nasal swabbing is to be performed prior to all inpatient stays and may be done at any time during the study based on subject clinical presentation or changes to local pandemic status or health directives. Results must be negative for the subject to be eligible for the study.

6.8. Vital Signs

Vital signs, including systolic (SBP) and diastolic blood pressure (DBP), pulse, respiration rate, and oral temperature (includes height, weight, and BMI at the Screening Visit), are to be measured at the time points indicated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2

[MAD], and Table 4 for Food-effect Cohort). Vital signs (except for height) will be monitored periodically during and following study drug administration. The investigator may repeat the vital signs if deemed appropriate.

Subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. When possible, blood pressure should be taken in the non-dominant arm throughout the study, using the same methodology (automated or manual). Repeat measures and more frequent monitoring can be implemented for clinically significant changes in blood pressure or heart rate.

On Day -1, the Active Stand Test (also known as the National Aeronautics and Space Administration [NASA] 10-Minute Lean Test) will be conducted. To perform the Active Stand Test, subjects should rest supine for 5–10 minutes to establish a baseline heart rate and blood pressure. Once the baseline heart rate and blood pressure are recorded, the subject must stand upright against a wall, with heels placed approximately 2 inches (5 cm) away from the wall, allowing for a slight backward lean. Once the subject is in position, measure heart rate and blood pressure every 2 minutes (+/- 30 seconds) for 10 minutes total. The subject should be instructed to avoid speaking or moving while conducting the Active Stand Test.

In addition, orthostatic vital signs will be conducted in Part 2 [MAD] according to the timepoints indicated in the SOA (Table 3).

6.9. Ophthalmologic Examinations

Ophthalmologic examinations will be performed at the time points indicated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort) and will consist of routine visual acuity and funduscopic examination.

6.10. Colonic Transit Test

SITZMARKS® is a diagnostic test indicated for aiding in the evaluation of colonic motility.

The SITZMARKS® capsule, for use in adult and pediatric subjects, will be dispensed for oral intake during study Part 2 (MAD).

Assessments will occur during the following study visits:

- Screening period: To assess subject eligibility.
- Treatment period Days 2–7: To evaluate colonic motility after dosing.

Procedures are as follows:

- On the first day of the test (any time during screening period and study Day 2, between study drug BID dosing), subjects will take one SITZMARKS® capsule by mouth with water. No laxatives, enemas, or suppositories may have been taken during the 5 days immediately preceding administration of the capsule.
- A flat plate abdominal X-ray will be taken on the **fifth day after capsule administration** (screening period and study Day 7) to determine the location and extent of elimination of the radiopaque markers.

Results will be assessed as follows:

- Subjects who expel at least 80% (19 or more) of the markers have grossly normal colonic transit.
- When remaining markers are scattered about the colon, condition is most likely hypomotility or colonic inertia.
- When remaining markers are accumulated in the rectum or rectosigmoid, the condition is most likely functional outlet delay, e.g., internal rectal prolapse, anismus.

Note: Subjects who do not expel at least 80% of the markers after 5 days of capsule intake during the screening period will be excluded from study participation.

6.11. Waist Measurement

For the MAD portion of the study, subjects' waists will be measured according to the timepoints designated in Table 3 for Part 2 [MAD]. The waist measurement should be recorded to the nearest tenth (in inches) by following the instructions listed below:

- Locate the bottom of the ribs and the top of the hips
- Place a tape measure around the middle at a point halfway between these two points (just above the belly button)
- Make sure the tape pulled tight, but is not digging into the skin
- Ask the subject to breathe out naturally and record the measurement

6.12. Food Consumption Measurement

An estimate measurement (e.g. percentage) of the subjects' food intake will be recorded during their 10-day residency period at the study site for the Part 2 [MAD] according to the frequency listed in Table 3. The measurement will be estimated by using 25% increments of the meal consumed.

6.13. Safety Laboratory and Pregnancy Testing

Clinical laboratory testing will be performed at the time points designated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort). Samples for safety laboratory testing are to be collected following a minimum 8-hour fast. Subjects will be in a seated or supine position during blood collection. Clinical laboratory testing (hematology with differential, serum chemistry, coagulation, and urinalysis) will be performed using standard methods.

Also, for females of childbearing potential, blood or urine human chorionic gonadotropin pregnancy tests will be performed at Screening and at the time of admission to the clinic (Day -1). Laboratory tests are listed in Table 7.

Table 7: Clinical Laboratory Tests

Hematology: • Hematocrit • Hemoglobin • Platelet count • RBC count • WBC count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	**Serum Chemistry**: • Glucose* • BUN • Creatinine • Total bilirubin • AST • ALT • GGT • Alkaline phosphatase • Creatine kinase • Total protein • Lactate dehydrogenase • Direct bilirubin • Sodium • Potassium • Total CO_2 • Chloride • Calcium • Inorganic phosphate • Magnesium • Insulin (Part 2)
Coagulation: • PT/INR • PTT	**Liver Function:** • Albumin • Globulin
Urinalysis: • Color • pH • Specific gravity • Protein • Glucose • Nitrates • Ketones	**Lipid Panel:** • Cholesterol • Triglycerides • HDL • LDL
Urine Drug Screen: • Amphetaminies • Barbiturates • Opiates • Benzodiazepines • Cocaine metabolites • Cannabinoids	**Immunoassays:** • Serum tryptase • Plasma histamine

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell

Serum hCG, as appropriate, at Screening and urine hCG at the time of study center admission and EOS. Females of non-childbearing potential due to menopause must have menopausal status confirmed by a serum FSH test at Screening.

*Note: Blood glucose levels will be monitored on specified study days during Part 2 when serum chemistry is not required. Please refer to Table 3.

6.13.1. Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample handling will be provided in the Laboratory Manual.

Biological material will be stored and secured in a way that assures that unauthorized access is prohibited and the samples are not lost, deteriorated, or accidentally or illegally destroyed. Details for storage and shipping will be provided in the Laboratory Manual.

6.14. Dispensing Study Drug

Following Screening and reconfirmation of eligibility at the time of clinic admission, subjects will be randomized according to the study center's SOPs. Using the randomization code, the onsite pharmacist will prepare and deliver the appropriate, blinded study drug to the study center for dosing.

6.15. Pharmacokinetics

The exact date and time of PK sample collection is to be documented in the eCRF.

6.15.1. Part 1 (SAD)

Blood samples will be collected prior to and following administration of the single oral dose of ARN-75039 or placebo at the following time points:

- Day 1 predose (within 60 minutes before dosing), and at 15 minutes (± 2 mins) 30 minutes (± 2 mins), then ± 10 mins at 1, 2, 4, 6, and 12 hours after dosing, then subsequently on Day 2 (24 hrs ± 1 hr), Day 3 (48 hrs ± 1 hr), Day 4 (72 hrs± 1 hr), Day 8 (168 hrs (± 24 hrs)) and EOS at approximately the same time as the dose of study drug was administered.

6.15.2. Part 2 (MAD)

Blood samples will be collected prior to and following administration of repeat doses of ARN-75039 or placebo at the following time points:

- PK assessments should be performed on Day 1 predose (within 60 minutes before dosing) and Day 10 predose (within 60 minutes before dosing), and at 30 minutes (± 2 mins), then ± 10 mins at 1, 2, 4, 6, 8, 10 (prior to second daily dose), 12, 14 and 24 hours after the initial morning dose. A pre-dose sample and a sample 6 hours after dosing should be collected on Days 2 and 8, and a pre-dose sample should be collected on Day 3. (Subjects will be discharged on Day 11 after collection of the 24-hour post-dose PK sample.) A sample should also be collected on Days 17 and 39 (EOS).

6.15.3. Food Effect Cohort(s)

Blood samples will be collected prior to and following administration of each ARN-75039 or placebo at the following time points:

- Day 1 predose (within 60 minutes before dosing), and at 15 minutes (± 2 mins), 30 minutes (± 2 mins), then ± 10 mins at 1, 2, 4, 6, and 12 hours after dosing, then subsequently on Day 2 (24 hrs ± 1 hr), Day 3 (48 hrs ± 1 hr), Day 4 (72 hrs± 1 hr), Day 8 (168 hrs (± 24 hrs)) and EOS at approximately the same time as the dose of study drug was administered.

6.16. Discharge from the Study Center

Subjects are to be discharged from the study center as indicated in the SOA (Table 2 for Part 1 [SAD], Table 3 for Part 2 [MAD], and Table 4 for Food-effect Cohort).

The actual date and time of discharge from the study center will be collected in the source documents and transcribed into the eCRF.

6.17. Adverse and Serious Adverse Events

6.17.1. Definition of Adverse Events

6.17.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after the start of study drug administration through the EOS visit following the cessation of treatment, whether or not they are related to the study, must be recorded in the eCRF.

6.17.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- Is life-threatening

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

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

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity

  The term disability means a substantial disruption of a person’s ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important

  Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

All SAEs that occur after the start of study drug administration through the EOS visit following the cessation of treatment, whether or not they are related to the study, must be recorded in the eCRF and other applicable databases.

6.17.1.3. Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (Investigator's Brochure). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

6.17.1.4. Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests.
- Leads to discontinuation of investigational product.
- Has accompanying or inducing symptoms or signs.
- Is judged by the Investigator as clinically significant.

6.17.1.5. Treatment-Emergent Adverse Events

An AE will be considered treatment-emergent if the onset date and time is after study drug administration or if the AE is present at baseline but worsens in intensity or is subsequently considered drug-related by the Investigator after study drug administration.

6.17.2. Relationship to Study Drug

The Investigator must use his/her medical judgment to assess the relationship of the TEAE to study drug. Even if the Investigator feels there is no relationship to study drug, the TEAE is to be reported.,

- Not Related: A TEAE that does not follow a reasonable temporal sequence from administration of the study drug, or that could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- Unlikely Related: A TEAE that is doubtfully related to administration of the study drug because the establishment of a causal relationship is considered biologically and physiologically highly improbable, though it may follow a reasonable temporal sequence from administration of study drug.
- Possibly Related: A TEAE that follows a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the study drug), that could not exclude the possibilities of the study drug (e.g., existence of similar reports attributed to the suspected study drug and its analogues, reactions attributable to the pharmacological effect), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
- Probably Related: A TEAE that follows a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the study drug), and that could exclude the possibilities of factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment, other than the study drug.
- Definitely Related: A TEAE considered to be undeniably related to the administration of study drug. Factors to be taken into consideration when assigning a definite relationship include whether the TEAE:
  - Follows a clear temporal sequence compared to administration of study drug.
  - Could not be possibly explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
  - Disappears or decreases on cessation or reduction in dose of study drug.
  - Reappears or worsens when study drug is re-administered.
  - Follows a response pattern known to be associated with administration of study drug.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible, "probable", or "definite", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

6.17.3. Severity

The intensity of each AE is to be assessed by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0:

- (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 6.17.1.2. An AE of severe intensity may not be considered serious.

6.17.4. Recording Adverse Events

AEs spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the first study drug dose until the EOS visit. Serious Adverse Event information will be collected from provision of informed consent through the EOS visit.

The AE term should be reported in standard medical terminology when possible.

For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

6.17.5. Pregnancy

Should a pregnancy occur in a female subject or the partner of a male subject, it must be reported and recorded on the pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be documented and any live births are to be followed for 1 month.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

6.17.6. Adverse Events of Special Interest

All AEs and SAEs that occur during the study will be reported and investigated. However, because of observations of early gastrointestinal (GI) symptoms in animal studies (e.g., severe malnutrition due to reduced food consumption and body weight loss observed in rats that received ARN-75039 at doses ≥2× the NOAEL), and skin symptoms (e.g., grade 2 pruritus) subjects in this study should be monitored for any new onset or worsening of GI and skin-related signs and symptoms.

For Part 2 of the study, the following events will be considered AEs of special interest (AESIs):

- GI-related: Nausea, vomiting, abdominal pain, onset of constipation/diarrhea (e.g., changes in frequency and stool consistency of bowel movements), loss of appetite, and weight loss.
- Skin-related: body pruritus (e.g., generalized), skin rash

An AESI may be serious or nonserious (e.g., meeting regulatory criteria definition). Such events will require further investigation to better characterize and understand them. Even if not meeting the "seriousness" criteria to be reported as SAE, these events must be assessed for severity per Section 6.17.3 and relationship to study drug similarly as for SAEs (Section 6.17.2).

Any AESI deemed as related (e.g., definitely, probably or possibly), greater than grade 1 or severe (if not included in the NCI CTCAE) (as assessed by the Principal Investigator or designee) **will require discontinuation of dosing of ARN-75039** (and follow-up until resolution).

6.17.7. Reporting Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 6.17.1.2). If the AE is considered serious, the Investigator should report this event to the Sponsor's Medical Monitor as outlined below and also to the Institutional Review Board (IRB) according to its SOPs.

If the Investigator detects an SAE in a study subject after the last scheduled follow-up visit, and considers the SAE related or possibly related to prior study treatment, the Investigator should report it to the Sponsor's Medical Monitor.

All information about SAEs will be collected and reported via subject report, relevant source document request and review, and SAE report entry within the eCRF. (Subject and Sponsor's Medical Monitor contact information will be contained in the investigational site file.) The Investigator should send the initial SAE report to the Sponsor's Medical Monitor within 24 hours of becoming aware of the SAE. At minimum, the initial SAE report should include the following information:

- Event
- Study code
- Subject number, initials, and date of birth
- Investigational product

- Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and for reported deaths, the Investigator should supply the Sponsor's Medical Monitor and the IRB with any additional requested information (e.g., autopsy reports, terminal medical reports).

The original SAE form and relevant source documents should be kept at the study site. The Sponsor or its designee will be responsible for determining reporting timelines and reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs that are ongoing at the Follow-up visit should be followed until resolved.

Arisan or qualified designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB of these additional SAEs.

6.18. Concomitant Medication Assessments

All prescription and OTC medications, herbals, and supplements taken by subjects during the study (i.e., from signing the ICF through the EOS visit) must be documented on the source document and transcribed into the eCRF.

7. STATISTICS

7.1. General Considerations

This is a Phase 1 study; as such, none of the endpoints are sufficiently powered to demonstrate a robust difference between cohorts. The cohort size has been selected in accordance with standard designs for Phase 1 assessments of safety, tolerability, and PK.

Data will be described and analyzed using the SAS System, Version 9.4 or higher (SAS Institute Inc., Cary, NC, SAS System). Individual subject data will be presented in subject data listings. Descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) will be presented for continuous data. For categorical data, frequency and percentage of subjects in each category will be presented.

The primary analysis will describe the incidence of adverse events and laboratory abnormalities.

7.2. Missing, Unused, and Spurious Data

All available safety and PK data will be included in data listings and summary tabulations. No imputation of values for missing data will be performed.

7.3. Subject Disposition

Reasons for study discontinuation will be listed on a per-subject basis, and, as warranted by the data tabulated.

7.4. Analysis Populations

All PK analysis will be based on the PK Population, which includes all subjects who receive any amount of ARN-75039 and have sufficient data to be included in the PK analysis postdose concentration-time data to determine at least 1 PK parameter.

All safety analyses will be based on the Safety Population, which includes all subjects who receive at least 1 dose of study drug.

7.5. Demographics and Baseline Characteristics

Demographic information will include age, sex, ethnicity, race, height and weight. All demographic information will be summarized by dosing cohort and treatment arm.

7.6. Extent of Exposure

Descriptive statistics for subject treated, including, for Part 2, the number of doses received and cumulative dose given, will be presented. A by-subject listing of study drug dosing data will be presented.

7.7. Concomitant Medications

All concomitant medications administered will be presented in a data listing.

7.8. Safety Analysis

Safety will be assessed by evaluation of AEs, physical examinations, clinical laboratory evaluations, ECGs, ophthalmologic examination findings, and vital signs measurements. AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 25.1 [released September 2022] or the current version). The occurrence of TEAEs and AESIs will be presented by body system and preferred (coded) term by dosing cohort in each study part. Additionally, AEs and AESIs will be presented for each dosing cohort and treatment arm by relationship and by severity with the most closely related or most severe presented for events that occurred more than once. A listing of SAEs will be provided, if applicable.

Physical examination findings will be presented as normal, abnormal for each day by dosing cohort and treatment arm.

The overall interpretation of the ECG result will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) for each visit, by dosing cohort and treatment arm. Descriptive statistics will be presented for the ECG measurements collected at each visit. Additionally, the changes between ECGs will be calculated, and descriptive statistics will be presented for each dosing cohort by treatment arm.

For the continuous laboratory parameters, descriptive statistics will be presented for each visit and for the changes from baseline to each visit by dosing cohort and treatment arm. Additionally, parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects will be presented by dosing cohort and treatment arm.

For each vital sign measurement recorded at each visit, descriptive statistics will be presented for each dosing cohort by treatment arm. The changes from Day -1 to each subsequent visit will be calculated and descriptive statistics will be presented.

7.9. Pharmacokinetic Analyses

Plasma ARN-75039 concentrations will be determined at all pre- and postdose time points.

The following PK parameters will be computed at minimum from plasma concentration data:

- Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{0-t})
- Area under the concentration-time curve from time 0 to the end of dosing interval (AUC_{0-tau})
- Area under plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- Maximum observed plasma concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Terminal elimination rate constant (λz)
- Terminal elimination half-life ($t_{1/2}$)

- Apparent clearance after extravascular administration (CL/F)
- Apparent volume of distribution during the terminal phase after extravascular administration (V_Z/F)

Plasma ARN-75039 concentrations and non-compartmental PK parameters will be tabulated by dose cohort using descriptive statistics. Tabulated multiple-dose PK results will be presented. Individual elapsed sampling times will be used in the PK analysis. C_{max} and t_{max} will be obtained directly from the experimental observations. AUC_{0-t} will be calculated using the linear trapezoidal rule.

For analyses of the food effect on the PK of ARN-75039, subjects will be considered evaluable if they receive study drug in each treatment period according to their randomized assignment.

Individual patient concentration-time data will be listed and displayed graphically on the linear and log scale. The concentration-time data will be summarized descriptively in tabular and graphical format (linear and log scale).

PK parameters estimated using noncompartmental methods. Such estimates will be listed and summarized descriptively in tabular and graphical format.

For selected PK parameters (e.g., C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$), comparisons between the fed and fasted conditions will be made.

Time to maximum observed plasma concentration of ARN-75039 (t_{max}) will be summarized for the fed and fasted conditions using descriptive statistics and graphical displays. Individual subject differences for t_{max} between the fed and fasted condition will be calculated; symmetric nonparametric confidence interval for the median difference will be provided. Inferential comparison of t_{max} between the fed and fasted condition will be made using Wilcoxon's signed rank test.

Additional details regarding PK analyses will be documented in a formal Statistical Analysis Plan.

7.10. Interim Analysis

An interim analysis of safety and PK data from Part 1 (SAD) was conducted to support additional regulatory submissions. A detailed description of data analyses and statistical methods will be outlined separately in the Statistical Analysis Plan.

8. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

8.1. Study Monitoring

Before an investigational site can enter a patient into the study, an initiation visit will be conducted at the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Arisan or its representatives. This will be documented in a Clinical Study Agreement between Arisan and the investigator.

During the study, monitoring personnel will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Arisan.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Arisan and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

8.2. Audits and Inspections

Authorized representatives of Arisan, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Arisan audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact Arisan or designee immediately if contacted by a regulatory agency about an inspection.

8.3. Access to Source Documentation

Local regulatory agencies and the Defense Threat Reduction Agency (DTRA) of the US Department of Defense (DoD) may request access to all study records, including source documents, for inspection and copying, in keeping with US regulations. The Investigator should immediately notify the Sponsor of any upcoming regulatory agency inspections. The Sponsor may also perform an audit of the data if deemed necessary.

The Investigator will be responsible for the accuracy of the data entered in the eCRFs. The Investigator will permit designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRFs.

8.4. Data Generation and Analysis

This study will be performed in accordance with regulatory requirements outlined in 21 Code of Federal Regulations (CFR) Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11 as well as the ICH GCP E6 Guidelines. The study monitor will meet with the Investigators and staff shortly before the start of the study to review the procedures for study conduct and documentation. During the study, the monitor will visit the study site to verify record keeping and adherence to the protocol. eCRFs will be used for the study. The monitor will conduct 100 percent source document verification by comparing the eCRFs with the source documents to ensure consistency. Edit check programs, other forms of electronic validation, manual listings and a query process will be executed to verify the accuracy of the database. A full audit trail of data changes will be maintained. Access to all source documentation will be made available for monitoring and audit purposes.

8.5. Retention of Data

All source documents (e.g., ICFs, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and study drug dispensing/disposition records) that support data in the eCRFs of each study subject must be retained in the files of the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements.

If the Investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor or designee must be notified in writing of the name and address of the new custodian, prior to the transfer.

9. ETHICS

9.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the Bioethics policies of Arisan or designee.

9.2. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB as appropriate. In addition, the Office of Human Research Oversight (OHRO) must approve in writing prior to implementation. The investigator must submit the written approvals to Arisan or designee before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB and OHRO of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB and OHRO upon receipt of amendments and annually, as local regulations require. Any substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the OHRO for approval prior to implementation. The OHRO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications, significant change in study design, or a change that could potentially increase risks to subjects, as noted at https://mrdc.health.mil/index.cfm/collaborate/research_protections/hrpo.

The Principal Investigator is also responsible for providing the IRB and the OHRO with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Arisan or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious ADRs will be provided to the IRB according to local regulations and guidelines, and to the OHRO.

9.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

10. PUBLICATION POLICY

All information concerning ARN-75039, Sponsor operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study and must not use it for other purposes without the Sponsor's written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of ARN-75039 and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

All publications and presentations must be approved in advance by the Sponsor, in its sole discretion. Subsequently, the Investigator may publish results from the study in compliance with their agreement with the Sponsor.

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