PROTOCOL ARN-75039-103

A COMPARATIVE, RANDOMIZED, TWO-PERIOD, CROSSOVER STUDY TO COMPARE PHARMACOKINETIC PROPERTIES OF ARN-75039 TABLETS WITH EXCIPIENTS TO NEAT ARN-75039 IN HYDROXYPROPYL METHYLCELLULOSE (HPMC) CAPSULES IN HEALTHY ADULT PARTICIPANTS UNDER FED CONDITIONS

Version 3.0 (29 January 2025)

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Arisan Therapeutics, Inc.

Sponsor's Authorized Officer: Ken McCormack, PhD

29-Jan-2025

Arisan Therapeutics, Inc. | Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ARN-75039. I have read Protocol ARN-75039-103 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.

Frank Lee

Printed Name of Investigator

Signature of Investigator

29-Jan-2025

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Protocol v1.0	08 July 2024 (not implemented)
Protocol v2.0	22 November 2024 (not implemented)
Protocol v3.0	29 January 2025

Amendment 3.0, 29 January 2025

Overall Rationale for the Amendment:

The Sponsor has made the following substantial amendment to the protocol as reflected in the Schedule of Assessments (Table 1) and text throughout the protocol:

Section # or Name	Description of Change	Brief Rationale
Procedures in Case of Emergency	Updated name and phone number for Clinical Study Leader	To reflect change in study personnel
Synopsis, 3.1 Overall Study Design	Changed timing of admission to the study site from the evening of Day -1 to the morning of Day -1.	To allow for more time to complete Day -1 procedures
	Changed length of screening period from up to 14 days to up to 21 days, with total study participation changed from approximately 50 days to approximately 57 days.	To allow for more time to complete screening procedures
	Changed rules for study drug discontinuation due to a study drug-related treatment-emergent adverse event.	To improve subject retention
	Added $C_{min0-24}$ as a primary endpoint	To improve pharmacokinetic analysis
Synopsis, 4.1 Participant Inclusion Criteria	Changed requirement for confirmation of post-menopausal status (in applicable females) from follicle stimulating hormone (FSH) of ≥40 to 'based on reference laboratory ranges.'	To accommodate the reference ranges of the laboratory used
	Added that "Males must agree to not donate sperm and to use condom and spermicide ***in combination with any of the means of contraception for their female partners detailed in Section 5.6.2***."	To ensure consistency of contraception requirements
	Added requirement for subjects to be able to consume a standard meal (400-600 Calories) within 30 minutes	To optimize pharmacokinetic analysis
Synopsis, 4.2 Participant Exclusion Criteria	Removed "Positive test for SARS-CoV-2 infection on Day -1."	To reflect current institutional procedures

Section # or Name	Description of Change	Brief Rationale
Synopsis, 5.2 Treatments Administered	Specified that meal prior to study drug dose will be a standard meal of approximately 400–600 Calories.	To standardize pre-dose meal
	Added summary of tablet prototype 1 formulation characteristics and pharmacokinetics.	To ensure consistency with protocol body
	Added summary table of tablet prototype 5 stability after one month.	To ensure consistency with protocol body
Schedule of Assessments	Added that Day 36 Follow Up Phone Call has +/- 2-day visit window and is required for Early Termination subjects.	To minimize protocol deviations and to clarify early termination procedures
	Added vital sign assessments on Days 2, 3, 4, and 5 of treatment Periods 1 and 2.	To improve safety monitoring
	Added vital sign Pre-dose assessment window, a 96-hour post-dose assessment, and clarified that the 16-hour Period 1 Day 1 vitals may be combined with the pre-dose Period 2 Day 1 timepoint.	To minimize protocol deviations
	Changed pregnancy test from urine test after serum test at Screening to all serum tests.	To reflect current institutional procedures
	Removed SARS-CoV-2 test (at Admission visit).	To reflect current institutional procedures
	Added that electrocardiogram will be performed at Admission, 24, 48, and 72 hours post-dose as well as at End of Active Treatment visits.	To improve safety monitoring
	Added a 96-hour post-dose pharmacokinetics assessment and clarified that the 16-hour Period 1 Day 1 vitals may be combined with the pre-dose Period 2 Day 1 timepoint.	To improve pharmacokinetics assessment
	Specified that drug test will be by urine and alcohol test will be by breath	To clarify test types
5.3 Selection and Timing of Dose for Each Participant	Specified that meal prior to study drug dose will be a standard meal of approximately 400–600 Calories.	To standardize pre-dose meal
5.6.2 Contraception	Added that "***Males must agree to not donate sperm and to use condom and spermicide*** in combination with any of the above means of contraception for their female partners ***during sexual intercourse from the time of the first study drug administration and for 90 days following the last dose of study drug.***"	To ensure consistency of contraception requirements
6.4 Electrocardiograms	Specified timing of ECGs.	To ensure consistency with Schedule of Assessments

Section # or Name	Description of Change	Brief Rationale
6.5 Alcohol and Drug Screening	Specified that drug test will be by urine and alcohol test will be by breath	To clarify test types
6.7 Vital Signs	Added that participants can be in a seated (or supine) position for vitals assessment	To clarify test procedure
6.8 Safety Laboratory and Pregnancy Testing	Specified timing of serum or urine pregnancy tests for women	To clarify timing of tests
	In Clinical Laboratory Tests table, added: • bilirubin, leukocytes, urobilinogen, blood, and microscopic analysis to urinalysis • eGFR to serum chemistry • breath alcohol test	To improve safety monitoring
6.13.6 Adverse Events of Special Interest (AESI)	Added that tachycardia has been observed in animal studies and that subjects in this study should be monitored for elevated heart rate.	To improve safety monitoring
	Clarified that an AESI may lead to discontinuation of ARN-75039 dosing, per the discretion of the Investigator and Sponsor Medical Monitor.	To clarify early termination procedures

The Sponsor also has made administrative updates not requiring a rationale.

PROCEDURES IN CASE OF EMERGENCY

Role in Study	Name	Address and Telephone number
Clinical Study Leader	Peter Van Wie, MPH, PhD Senior Project Manager	Frontage Clinical Services Inc. 200 Meadowlands Parkway Secaucus, NJ 07094 +1 201.469.5677
Responsible Physician	Dr. Frank Lee M.D., C.P.I. Executive Medical Director and Principal Investigator	Frontage Clinical Services Inc. 200 Meadowlands Parkway Secaucus, NJ 07094 +1 551.213.6664
Drug Safety Physician	Dr. Frank Lee M.D., C.P.I. Executive Medical Director and Principal Investigator	Frontage Clinical Services Inc. 200 Meadowlands Parkway Secaucus, NJ 07094 +1 551.213.6664
24-Hour Emergency Contact	Not Applicable	Frontage Clinical Services Inc. 200 Meadowlands Parkway Secaucus, NJ 07094 +1 551.213.6664

SYNOPSIS

Title of Study Protocol: A Comparative, Randomized, Two-Period, Crossover Study to Compare Pharmacokinetic Properties of ARN-75039 Tablets with Excipients to Neat ARN-75039 in Hydroxypropyl Methylcellulose (HPMC) Capsules in Healthy Adult Participants under Fed Conditions

Protocol Number: ARN-75039-103

Name of Sponsor Company: Arisan Therapeutics

Name of Investigational Product: ARN-75039 tablet and capsules for oral administration

Phase of Development: Phase 1

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To compare the pharmacokinetic (PK) properties of 300 mg ARN-75039 with excipients in tablet form to 300 mg neat ARN-75039 in HPMC capsules following oral administration under fed conditions	• PK parameters of 300 mg ARN-75039 with excipients in tablet form and 300 mg neat ARN-75039 in HPMC capsules, including but not limited to: o Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{0-t}). o Area under the plasma concentration-time curve from time zero to 24 hours post-dose (AUC_{0-24}). o Area under plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). o Maximum observed plasma concentration (C_{max}). o Minimum observed plasma concentration from time zero to 24 hours post-dose ($C_{min0-24}$) 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).
Secondary Objectives	**Secondary Endpoints**
• To provide additional information on the safety and tolerability of ARN-75039 administered orally in healthy participants	• 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), physical examinations, and vital signs.

Study Design:

ARN-75039-103 is a comparative, randomized, single-dose, crossover study to assess the PK, safety, and tolerability of neat ARN-75039 in hydroxypropyl methylcellulose (HPMC) capsules against ARN-75039 with excipients in tablet form administered by the oral route in healthy adult participants.

The safety assessments will include standard evaluations of vital signs, clinical laboratory values, and ECGs.

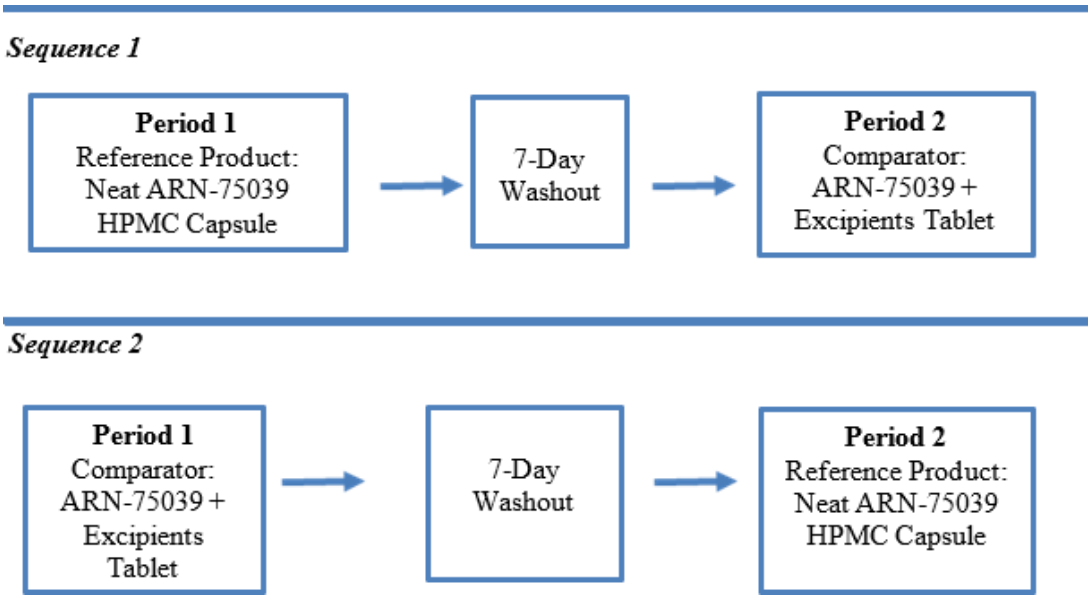
Pharmacokinetic analysis of HPMC capsules filled with neat ARN-75039 was assessed in dogs under both fed and fasted conditions whereby capsules were filled with neat ARN-75039 relative to the dog's weight prior to dosing at the equivalent of a 10 mg/kg dose. Mean C_{max} and AUC_{0-24} were 5.2- and 8.8-fold higher under fed conditions in dogs relative to fasted state conditions in dogs. Therefore, it was decided to dose participants in this study under fed state conditions.

Participants will be admitted to the study site on the morning of Day -1, prior to Period 1 study drug administration, and will remain on site until Day 15. Upon confirmation of eligibility, participants will be randomized into the study on Day 1. Study drug administration will be performed on the first day of Periods 1 and 2 (Study Days 1 and 8, respectively) with a 7-day washout period between the two periods. Participants will receive the randomized study drug in the morning following a meal. A total of 16 participants will be randomized 1:1 to the following two sequences:

- **Sequence 1:**
  - Period 1: 300 mg neat ARN-75039 in HPMC capsules (reference product)
  - Period 2: 300 mg ARN-75039 with excipients in tablet form (comparator)
- **Sequence 2**:
  - Period 1: 300 mg ARN-75039 with excipients in tablet form (comparator)
  - Period 2: 300 mg neat ARN-75039 in HPMC capsules (reference product)

A study schema is provided in Figure 1. A schedule of assessments is presented in Table 1.

Figure 1: Study Schema



Participants will be randomized 1:1 into one of two sequences in this comparative, single dose, crossover study.

Participation in the study will be conducted in the following 5 defined periods:

- **Screening Period:** The Screening Period begins upon completion of the informed consent form (ICF). During this period, participants will undergo baseline assessments to determine eligibility

for study participation. The Screening Period duration will be up to 21 days; it will end after all evaluations required to meet eligibility have been completed. If a participant meets all eligibility criteria, they will be offered enrollment into the study.

- **Admission to Study Site:** Participants will be admitted to the study site in the morning on the day prior to dosing of period 1 (Day -1). Participants that are eligible to participate in the study and are randomized into the study will remain at the study site until completion of the treatment period (Study Day 15).
- **Treatment Period:** This study consists of two treatment days separated by a 7-day washout period. The first treatment day will begin on Day 1 of Period 1 with administration of the first dose of study drug. The second treatment day will occur on the first day of Period 2 (Study Day 8). Following the dosing of the study drug on each treatment day, fifteen venous blood samples will be withdrawn via an indwelling cannula or by venipuncture at regular time intervals.
- **End of Active Treatment (Day 15 Discharge Visit or Early Termination (ET) Visit):** Upon successful completion of active treatment, participants will be discharged from the study site on Study Day 15. The Discharge Visit will include the completion of safety assessments, such as a physical examination, vitals, ECG recording, adverse event review, and clinical laboratory tests. Participants who complete both dosing days will be encouraged to complete all study visits. Participants who do not complete all study visits or terminate from the study prior to Day 15 will be asked to complete the Early Termination Visit within 1 day after withdrawal from the study.
- **Day 36 Telephone Follow Up Phone Call**: Participants will be contacted by phone on Day 36—i.e., 28 days following the last study dose administered on Day 8. The purpose of this follow-up call is to assess for any adverse events.

If a participant has a study drug-related Grade > 1 treatment-emergent adverse event (TEAE) during the Treatment Period, study drug dosing may be discontinued for that participant following discussion between the Investigator and Sponsor Medical Monitor. These participants will not be replaced. If a subject has a study drug-related 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. Discontinued participants experiencing a study drug-related TEAE will be asked to complete follow up study visits through the Day 36 Phone Call Follow Up. If a participant terminates early for a reason other than a study drug-related TEAE during the Treatment Period, the participant may be replaced. These participants will also be asked to complete follow up study visits through the Day 36 Phone Call Follow Up, unless they terminated their participation in the study prior to dosing. Study drug dose level modifications or dosing administration deviations outside the protocol-specified windows are not permitted during the Treatment Period.

Number of Participants Planned:

- 16 evaluable participants are planned for study participation
  - Participants withdrawn due to a study drug-related Grade >1 TEAE will not be replaced.
  - Participants withdrawn due to a study drug-related Grade 1 TEAE may be replaced.
  - Participants who are withdrawn due to a reason other than a study drug-related TEAE during the Treatment Period may be replaced as necessary to obtain 16 evaluable participants at the end of the clinical study.

Study Duration:

- Total study duration per participant is approximately 57 days:
  - Screening: Approximately 21 days

- Treatment Period: 14 days
- Day 15 Discharge Visit or Early Termination Visit: 1 day
- Day 36 Telephone Follow Up Call: 1 day

Eligibility:

Participants 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.

Re-Screening Criteria:

In the event a participant'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 participant can be considered eligible for the study. In the event a participant fails to meet the overall screening criteria, the participant may repeat the overall screening process once, and if the participant then meets all eligibility criteria, the participant will be considered eligible to enter the study.

Special Populations:

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. In addition, the Sponsor will attempt enroll ≥30% and ≤50% female subjects to ensure adequate representation of both sexes.

Inclusion Criteria:

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

1. Is male or female, age 18 to 45 years, inclusive, at Screening.
2. Body mass index (BMI) between 18 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; participants 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/1.73 m^2 at Screening.
6. Females of childbearing potential must practice effective contraception per national regulatory guidelines for clinical trials from Screening (see Section 5.6.2), throughout the study, and for 60 days after the last dose of study drug.
7. Females must have a negative pregnancy test at Screening and within 24 hours prior to dosing of study drug; for post-menopausal participants, a blood sample will also be tested for estradiol and follicle stimulating hormone (FSH) to confirm post-menopausal status based on reference laboratory ranges for post-menopausal status. Surgically sterile females are eligible; however, proof via medical records will be required.
8. Males must agree to not donate sperm and to use condom and spermicide in combination with any of the means of contraception for their female partners detailed in Section 5.6.2 during sexual intercourse from the time of the first study drug administration and for 90 days following the last dose of study drug. 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 sun protection factor [SPF] 75 or greater sunscreen when outdoors) during the study treatment period.
10. Able to consume a standard meal (400-600 Calories) within 30 minutes.

11. Able to provide informed consent.
12. Willing and able to comply with this protocol and be available for the entire duration of the study.

Exclusion Criteria:

Participants 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. Prior exposure to ARN-75039.
4. 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.
5. 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 Day 15 Discharge Visit.
6. Any female who is pregnant or breastfeeding, or any female who is planning to become pregnant during the study and safety follow-up period.
7. 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.
8. Inability to ingest all capsules of a multi-capsule dose within 5 minutes of ingestion of the first capsule.
9. Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening; participants with adequately treated HCV are eligible for enrollment.
10. Consumption of Seville oranges, grapefruit or grapefruit juice within 72 hours prior to Day 1 or during the study.
11. History of malignancy, except adequately treated basal cell carcinoma or in situ carcinoma of the uterine cervix.
12. Smoking cigarettes, cigars, cigarillos, or E-cigarettes.
13. Any reason or condition that, in the investigator's opinion, may compromise study participation, present a safety risk to the participant, 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 (including plasma) donation within 30 days before Screening.
16. Unwilling to consume a breakfast on study drug administration days.
17. History of:
    - Structural abnormality of the gastrointestinal (GI) tract or a disease or history of a condition that can affect GI motility.
    - Inflammatory bowel disease (even if treated and currently in remission).
    - 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.
    - Chronic idiopathic diarrhea.
18. 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. Participant 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. History of chronic/generalized pruritus and/or skin rash of unknown origin.
23. Participants with diagnosed Type 1 or Type 2 diabetes, or with a fasting blood glucose value > 125 mg/dL during the screening period.

Investigational Products, Dosage, and Mode of Administration:

Study drug is to be administered in the fed state, with participants served a standard meal (approximately 400–600 Calories), which must be consumed within 30 minutes prior to the scheduled study drug dose. Study drug will be administered orally with 240 mL or the smallest amount of water needed to swallow all the capsules.

ARN-75039 will be supplied to the clinical site in two formulations:

- Formulation A: Three 100 mg neat ARN-75039 HPMC capsules drug product (reference) once daily (QD) administered (300 mg dose total)
- Formulation B: Three 100 mg ARN-75039 tablet drug product (comparator) QD (300 mg dose total)

Oral Tablet Formulation Development

The reference drug product will be prepared by the onsite pharmacist or designee by dispensing the specified weight of drug substance and encapsulating it in an HPMC capsule prior to oral dosing. ARN-75039 reference drug substance and comparator drug product should be stored at 15–25°C. The comparator drug product (prototype 5) is manufactured initially as a dry blend with 33.6% w/w ARN-75039 along with intragranular excipients including 33.6% Prosolv SMCC 90 LM (silicified microcrystalline cellulose), 1.0% Aerosil 200 (Fumed Silica), 2.4% Ac-Di-Sol SD-711 (Croscarmellose sodium) and 1% Magnesium stearate.

The material is dry blended with Gerties Roller compactor whereby ribbons are generated with an average thickness of 1.75-1.92 mm. The ribbons are then granulated using a 20-mesh screen. To the dry granulated material additional extragranular excipients are added including 19.4% Prosolv, 2.4% Ac-Di-Sol SD-711 and 1.9% Magnesium stearate and the material added to Korsch XL100, 24 tablet press. After tablets are pressed, they are coated using 24" CompuLab Coater with 3.8% Opadry Titanium Free 276U110003 Green color and 1.0% Opadry II 85F19999 Clear Coat.

The PK of tablets having a highly similar formulation (Prototype 1 same excipients and dry blend step) was tested in dogs. The tablet formulation began with dry-blend including 40% ARN-75039, 40% Prosolv, 1.0% Aerosil 200, 2.5% Ac-Di-Sol SD-711 and 1.0% Magnesium stearate followed by extragranular excipients for tablet pressing of 12.0% Prosolv, 2.5% Ac-Di-Sol SD-711 and 1% Magnesium stearate. The formulation was changed to prototype 5 because picking was observed during tablet pressing of prototype 1.

A 100 mg tablet of protype 1 formulation and a prototype 5 formulation were orally delivered to dogs and compared to HPMC capsules filled with 100 mg neat ARN-75039 and the mean PK values are as follows:

Oral Dose	C_{max} ng/mL (mM)	T_{max} (h)	AUC_{0-24} (ng/mL*hr)	C_{min} 24 hr ng/mL (µM)	Clearance (mL/min/kg)	Vd (L/kg)
100 mg API Neat in HPMC capsule	4518	5	45453	369.1 (0.89)	4	4
100 mg tablet P1	5105	2	39211	335.6 (0.81)	4	7
100 mg tablet P5	5346	4	42542	399 (0.96)	5	-

Abbreviations: API = active pharmaceutical ingredient; HPMC = hydroxypropyl methylcellulose.

Prototype 5 stability after one month at both long-term (25°C/60% relative humidity [RH]) and accelerated (40°C/75% RH) stability is as follows:

Time Point		Long-term Stability (25°C/60%RH)	Accelerated Stability (40°C/75%RH)	Specification
Initial	--	100%		90–110% of Label Claim
1 Month	--	99.5%	100%	
Related Substances				
Initial	RRT 0.66	0.05%		• Report all impurities ≥ 0.05% area • Individual Unspecified Degradation Impurities NMT 0.5% area • Total Degradation Impurities NMT 5% area
	iPrBA	0.06%[1]		
	Total Impurities	0.0%[2]		
1 Month	RRT 0.53	0.05%	0.05%	--
	RRT 0.94	0.05%	<LOQ	--
	Total Impurities	0.1%	0.1%	--

Abbreviations: LOQ = limit of quantitation; NMT = not more than; RH = relative humidity; RRT = relative retention time

[1] iPrBA is a process impurity not a degradation impurity. Process impurities are reported but excluded from total degradation impurity calculations.

[2] Individual degradation impurities are reported to two decimal places. Total impurities are reported to one decimal place. RRT 0.66 rounds to 0.05% when reported to two decimal places but 0.0% when reported to one decimal place.

Statistical Methods:

The sample size has been selected in accordance with standard designs for Phase 1 assessments of PK, safety, and tolerability. The primary analysis will describe the PK characteristics of the two drug products. PK samples will be collected at pre-specified time points.

The PK parameters to be assessed include but are not limited to:

- C_{max} maximum plasma concentration
- $C_{min0-24}$ minimum plasma concentration from time zero to 24 hours post-dose
- t_{max} time of maximum plasma concentration
- λ_z terminal-phase rate constant
- $t_{½}$ elimination half-life
- AUC_{0-24} area under the plasma concentration-time curve from time zero to 24 hours post-

dosing

- AUC_{0-t} area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
- $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
- CL/F apparent clearance
- MRT mean residence time
- V_z/F apparent volume of distribution

The secondary endpoints 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 (MedDRA) (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. A detailed description of data analyses and statistical methods will be outlined separately in the Statistical Analysis Plan.

Date: 29 January 2025

Table 1: Schedule of Assessments

Procedure	Period	Screening Period	Admi-ssion	Period 1						Period 2								End of Active Treatment		Follow Up Phone Call
	Visit	Screening	P1D-1	P1D1	P1D2	P1D3	P1D4	P1D5	P1D6	P2D-1	P2D1	P2D2	P2D3	P2D4	P2D5	P2D6	P2D7	Discharge	ET	Day 36 +/- 2 days
	Study Day	Days -21 to -1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	ET[a]	
Informed consent		X																		
Eligibility criteria review		X	X																	
Randomization				X																
Demographics[b]		X																		
Medical and surgical histories		X	X																	
Vital signs[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[d]		X			X							X						X	X	
Pregnancy test[e]		X	X															X	X	
Concomitant medications		X	X															X	X	
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]		X	X	X	X	X	X			X	X	X	X	X				X	X	
Hematology[g]		X	X		X					X		X						X	X	

Procedure	Period	Screening Period	Admission	Period 1						Period 2								End of Active Treatment		Follow Up Phone Call
	Visit	Screening	P1D-1	P1D1	P1D2	P1D3	P1D4	P1D5	P1D6	P2D-1	P2D1	P2D2	P2D3	P2D4	P2D5	P2D6	P2D7	Discharge	ET	Day 36 +/- 2 days
	Study Day	Days -21 to -1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	ET[a]	
Drug test (urine) alcohol test (breath)		X	X																	
Serology[h]		X																		
Serum chemistry and coagulation[g]		X	X		X					X		X						X	X	
Urinalysis[g]		X			X							X						X	X	
Admission to site			X																	
Study drug administration				X							X									
PK (plasma)[i]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge from site																		X	X	

Abbreviations: D = Day(s); ECG = electrocardiogram; ET = early termination; HbsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; min = minute(s); PK = pharmacokinetics.

[a] If participant withdraws from the study prematurely, the ET visit is to be conducted within 1 days after withdrawal. Day 36 Follow Up Phone Call is also required for ET subjects.

[b] Includes participant'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. Participant must be seated or in a supine 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 study drug administration days: Pre-dose (-60 min), and 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 2 (±10 min), 4 (±10 min), 8 (±10 min), 12 (±10 min), 24 (±30 min), 48 (±30 min), 72 (±60 min), 96 (±60 min), 120 (±60 min), 144 (±60 min), and 168 (±60 min) hours post-dose. The 168-hour post dose P1D1 vitals may be combined with the pre-dose P2D1timepoint, in which case, the P2D1 pre-dose vital signs should be collected within 60 minutes prior to dosing.

[d] Physical examination will be complete at Screening and symptom-directed for all other study days at the PI's discretion. At a minimum, the complete physical examination should include general appearance, skin, head, ears, eyes, 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 participant complaints or changes from baseline

as clinically indicated. A symptom-directed (or complete, based on the PI's discretion) physical examination should be completed 24 hours post-dose on Study Days 2 and 9.

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

[f] Triplicate ECGs will be performed at screening, admission, dosing Day 1 in each period, and end of treatment (discharge or early termination). Triplicate ECGs will be measured at pre-dose (within -90min), and post dose 1hr (±20 min), 3hr (±20 min), 6hr (±20 min), 8hr (±20 min), 24 hr (±60 min), 48 hr (±60 min), and 72 hr (±60 min) post dose (for both doses) triplicates measurement will be taken within 5 minutes apart. Subjects should be at rest for 10 minutes prior to ECG. For participants that withdraw or are terminated early from the study, ECG will be performed at the ET visit.

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

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

[I] PK assessments should be performed on Day 1 of Periods 1 and 2 Pre-dose (hour 0) (within 60 mins prior to dosing), 0.5 hour (+/- 2 mins), 1 hour (+/- 5 mins), 2 hours (+/- 5 mins), 3 hours (+/- 10 mins), 4 hours (+/- 10 mins), 6 hours (+/- 10 mins), 8 hours (+/- 10 mins), 10 hours (+/- 10 mins), 12 hours (+/- 10 mins), 24 hours (+/- 60 mins), 48 hours (+/- 60 mins), 72 (+/- 60 mins), 96 (+/- 60 mins), 120 (+/- 60 mins), 144 (±60 min), and 168 hours (+/- 60 mins) relative to morning dose and at Discharge or ET visit at approximately the same time (+/- 1 hr) as the dose of study drug administration. The 168-hour post-dose P1D1 may be combined with the pre-dose PK collection for P2D1. P2D7 PK will be collected 144 (±60 min).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF 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_{0-4h}	area under the plasma concentration-time curve from time zero to 4 hours post-dosing
AUC_{0-24h}	area under the plasma concentration-time curve from time zero to 24 hours post-dosing
AUC_{0-t}	area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
BCRP	breast cancer resistance protein
BMI	body mass index
BUN	blood urea nitrogen
CAPV	Chapare virus
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
CO_2	carbon dioxide
C_{max}	maximum plasma concentration
$C_{min0-24}$	minimum plasma concentration from time zero to 24 hours post-dose
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
eGFR	estimated glomerular filtration rate
EOS	end of study

Abbreviation or Specialist Term	Definition
ET	early termination
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
f_u	unbound fraction
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GP	glycoprotein
GTOV	Guanarito virus
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
iNa	inward sodium current
iNa-L	inward sodium current – late
iNa-P	inward sodium current – peak
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LASV	Lassa virus
LCMV	Lymphocytic Choriomeningitis virus
LHF	Lassa hemorrhagic fever
LUJV	Lujo virus
MACV	Machupo virus
MedDRA	Medical Dictionary for Regulatory Activities
MRSD	maximum recommended starting dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level

Abbreviation or Specialist Term	Definition
OAT	organic anion transporter
OCT	organic cation transporter
OHRO	Office of Human Research Oversight
OTC	over-the-counter
P-gp	P-glycoprotein
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
QTcI	heart-rate corrected QT interval
QTcVW	QT interval Van der Waters correction
RBC	red blood cell
SABV	Sabia virus
SAD	single ascending dose
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOA	schedule of assessments
SOP	standard operating procedure
SPF	sun protection factor
$t_{½}$	elimination half-life
TCRV	Tacaribe virus
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 numerous 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 90% effective concentration (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

It is unknown whether neat ARN-75039 in HPMC capsules or ARN-75039 with excipients in tablet form provides improved pharmacokinetic (PK) exposure and greater anti-viremia activity. 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 PK exposure to the suspension formulation.

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). ARN75039 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 vitaminv-E-D-α-tocopherolt 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 plasma concentration-time curve from time zero to 4 hours post-dosing [$AUC_{0\text{-}4h}$]) 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 area under the plasma concentration-time curve from time zero to 24 hours post-dosing ($AUC_{0\text{-}24}$) 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- to 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 (area under the plasma concentration-time curve from time zero to time t [AUC_{0-t}]) 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_{0-t} values following administration of 100 and 300 mg/kg/day ARN-75039 on Day 1 and in AUC_{0-t} 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.

To support the current clinical study, 28-day definitive toxicology 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 nonclinical toxicology studies were conducted in compliance with United States (US) Food and Drug Administration (FDA) Good Laboratory Practice (GLP) regulations.

In rats, the 28-day NOAEL was 30 mg/kg. An additional 17-day (females) / 16-day (males) NOAEL of 50 mg/kg were also determined in this study. Based on these NOAEL values, a maximum recommended starting dose (MRSD) of 28.8 (rounded to 30) mg per day was calculated for the initial dose of the Phase 1 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 GLP dog repeat-dose oral toxicity studies, a 14-day NOAEL of 30 mg was determined. Initially ARN-75039 was administered to Beagle dogs once daily via oral gavage (5 mL/kg) at dosages of 0 (vehicle), 100, 300 and 1000 mg/kg/day beginning on Day 1. However, dose-limiting moribundity was encountered at all doses. Due to unanticipated evidence of dose-limiting moribundity noted during the first week of the dosing phase dogs were given a dosing holiday for 8–10 days and then subsequently administered ~30× lower doses (at 3, 10, and 30 mg/kg) for the remaining 14 days. All animals completed 14 days of the reduced dosing indicating that any toxic effects were reversible. Following the dose holiday/dose reduction, some ARN-75039-related clinical observations persisted, including diarrhea, emesis, and salivation. The incidence of these observations was greater at the high-dose level relative to mid- and/or low-dose levels, but none of the observations were considered adverse during the Day 15–28 dosing period. ARN-75039-related effects on body weight and food consumption at the lower

doses were comparable to vehicle control dogs. Ophthalmology and electrocardiography examinations were unremarkable. ARN-75039-related clinical pathology findings at the end of the dosing phase (Day 29) were limited to effects on hematology (reduced red cell mass, hematocrit and hemoglobin values and reduced reticulocytes in males only) at the high-dose level. Contrary to what was observed in rats, all dogs in all drug-dosed cohorts exhibited normal glucose. Target organs included effects on thymus and bone marrow. Mean thymus weight parameters were decreased (versus control) in females at all dose levels and in males at the high-dose level. The decreased thymus weights in several animals correlated microscopically with decreased lymphocytes. Bone marrow findings of minimal to mild decreased hematopoietic cellularity were noted in both sexes at all dose levels. The finding was characterized by increased adipose tissue and occasionally dilated bone marrow sinuses.

Under the conditions of this study, the NOAEL for ARN-75039 was considered to be 30 mg/kg/day (for 14 consecutive days). Systemic exposure (C_{max} and AUC_{0-24}) to ARN-75039 at the NOAEL on Day 28 was 18,300 ng/mL and 263,000 ng*h/mL, respectively, in males and 16,900 ng/mL and 261,000 ng*h/mL, respectively, in females.

In both rat and dog studies, gastrointestinal (GI)-related effects that included reduced food consumption, vomiting, loss of appetite and body weight were observed (≥100 mg/kg/day). None of the GI-related adverse effects 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.

1.2.4. 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 (50% inhibitory concentration [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, electrocardiogram (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 [QTcIQ (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- to 4-hour and 5- to 8-hour post-dose intervals at 100 and 300 mg/kg. At the 9- to 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 to 4 hour and 5- to 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 human ether-à-go-go-related gene (hERG) 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 ($Na_V1.5$) and calcium (Ca_V 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 $Na_V1.5$ (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 $Na_V1.5$ (Late) sodium ion channel current may be expected at free (f_u) plasma concentrations at or above the IC_{50} value of 0.55 µM (fu ≥ 0.23 µg/mL). $Na_V1.5$ channels mediate the inward sodium current (iNa) and induce fast depolarization, thereby initiating the excitation contraction coupling cascades in the cells. iNa -mediated by $Na_V1.5$ 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 $Na_V1.5$ channels fail to inactivate, contributing to increased late sodium current (iNa-L), cause congenital long-QT syndrome type 3 (LQT3) and the risk for arrhythmias (Ruan 2009). Several reports have shown that enhancing $Na_V1.5$ late current can lead to cardiac arrhythmias (Kistamásá 2021) and therefore, selectively inhibiting the $Na_V1.5$ late current may have anti-arrhythmic effects (Horváth 2020). Furthermore, blockade $Na_V1.5$-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 $Na_V1.5$ late current block of 17 µM vs 0.55 µM 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 cannabinoid 1 (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 CB_1 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-glycoprotein (P-gp) and breast cancer resistance protein (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 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.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To compare the pharmacokinetic properties of 300 mg ARN-75039 with excipients tablets (comparator) to 300 mg neat ARN-75039 in HPMC capsules (reference) following oral administration under fed conditions	• PK parameters of 300 mg ARN-75039 with excipients tablets and 300 mg neat ARN-75039 in HPMC capsules, including but not limited to: o Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{0-t}). o Area under the plasma concentration-time curve from time zero to 24 hours post-dose (AUC_{0-24}). o Area under plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). o Maximum observed plasma concentration (C_{max}). o Minimum observed plasma concentration from time zero to 24 hours post-dose $C_{max0-24}$. 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).
Secondary Objectives	**Secondary Endpoints**
• To provide additional information on the safety and tolerability of ARN-75039 administered orally in healthy participants.	• 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, ECGs, colonic transit time (biomarker), physical examinations, and vital signs.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

ARN-75039-103 is a comparative, randomized, single-dose, crossover study to assess the PK, safety, and tolerability of neat ARN-75039 in hydroxypropyl methylcellulose (HPMC) capsules against ARN-75039 with excipients in tablet form administered by the oral route in healthy adult participants. The safety assessments will include standard evaluations of vital signs, clinical laboratory values, and ECGs.

Pharmacokinetic analysis of HPMC capsules filled with neat ARN-75039 was assessed in dogs under both fed and fasted conditions whereby capsules were filled with neat ARN-75039 relative to the dog's weight prior to dosing at the equivalent of aa 10 mg/kg dose. Mean C_{max} and AUC_{0-24} were 5.2- and 8.8-fold higher in under fed conditions in dogs relative to fasted state conditions in dogs. Therefore, it was decided to dose participants in this study under fed state conditions.

Participants will be randomized into one of the following two sequences:

Sequence 1:

- Period 1: 300 mg neat ARN-75039 in HPMC capsules (reference product)
- Period 2: 300 mg ARN-75039 with excipients in tablet form (comparator)

Sequence 2:

- Period 1: 300 mg ARN-75039 with excipients in tablet form (comparator)
- Period 2: 300 mg neat ARN-75039 in HPMC capsules (reference product)

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

Participants will be admitted to the study site on the morning of Day -1, randomized to Period 1 study drug administration on Day 1, and will remain on site until study completion at Day 15. Participants will receive the randomized study drug in the morning following a meal. Participants will be dosed on Day 1 and Day 8 with a 7-day wash out period between the two dosing days. PK assessments will be performed according to the SOA (Table 1).

Participants that withdraw from active treatment or are terminated from the treatment period will undergo an Early Termination (ET) visit.

Participation in the study will be conducted in the following 5 defined periods, with a total study duration of approximately 57 days:

- **Screening Period:** The Screening Period begins when the informed consent form (ICF) is signed. During this period, participants will undergo baseline assessments to determine eligibility for study participation. The Screening Period duration will be up to 21 days; it will end after all evaluations required to meet eligibility have been completed. If a participant meets all eligibility criteria, they will be offered enrollment into the study.

- **Admission to the Study Center:** Participants will be admitted to the study site in the morning on the day prior to dosing of period 1 (Day -1) and will remain at the study site until study completion (Day 15). Upon admission to the study site, participants will be randomized into the study on Day 1 after the confirmation of eligibility.
- **Treatment Period:** This study consists of two treatment days separated by a 7-day washout period. The first treatment day will begin on Day 1 of Period 1 with administration of the first dose of study drug. The second treatment day will occur on the first day of Period 2 (Study Day 8). Following the dosing of the study drug on each treatment day, fifteen venous blood samples will be withdrawn via an indwelling cannula or by venipuncture at regular time intervals. Subjects will be discharged on Day 15.
- **End of Active Treatment (Day 15 Discharge Visit or Early Termination Visit):** Upon successful completion of active treatment, participants will be discharged from the study site on Day 15. The Day 15 Discharge Visit will include the completion of safety assessments, such as a physical examination, vitals, ECG recording, adverse event review, and clinical laboratory tests. Participants who complete both dosing days will be encouraged to complete all study visits. Participants who do not complete all study visits or terminate early from the study will be asked to complete the Early Termination Visit within 1 day after withdrawal from the study.
- **Day 36 Telephone Follow Up Phone Call:** Participants will be contacted by phone on Day 36—i.e., 28 days following the last study dose administered on Day 8. The purpose of this follow-up call is to assess for any adverse events.

If a participant has a study drug-related Grade > 1 TEAE during the Treatment Period, study drug dosing may be discontinued for that participant following discussion between the Investigator and Sponsor Medical Monitor. These participants will not be replaced. If a subject has a study drug-related 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. Discontinued participants experiencing a study drug-related TEAE will be asked to complete follow up study visits through the Day 36 Phone Call Follow Up.

If a participant terminates early for a reason other than a study drug-related TEAE during the Treatment Period, the participant may be replaced. These participants will also be asked to complete follow up study visits through the Day 36 Phone Call Follow Up, unless they terminated their participation in the study prior to dosing. Study drug dose level modifications or dosing administration deviations outside the protocol-specified windows are not permitted during the Treatment Period.

3.2. Justification for the Study Design

A randomized, comparative, crossover study was selected to eliminate participant variation and to improve precision of the PK characteristics of both study drug formulations with a smaller sample size. To compensate for the long half-life of the study drug and the relatively short washout period, additional PK timepoints were included to aid in modeling of the study drug clearance and elimination.

This clinical study is being performed in healthy participants 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.

3.3. Number of Participants

The sample size of 16 evaluable participants proposed for this study was not based on statistical analysis assessments but is judged to provide a sufficient dataset to be able to make direct comparisons in pharmacokinetic parameter estimates between the reference and test groups in this clinical study. Participants withdrawn due to a study drug-related Grade >1 TEAE will not be replaced. Participants who are withdrawn due to a study drug-related Grade 1 TEAE may be replaced. Participants who are withdrawn due to a reason other than a study drug-related TEAE during the Treatment Period may be as necessary to obtain 16 evaluable participants at the end of the clinical study.

3.4. Study Completion

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

The date of termination is the date of the last contact in which the participant's health status was assessed, or in cases where the participant 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.

3.5. 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 participants enrolled in the study.
- Failure of the Investigator to enter participants 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 PARTICIPANTS

This study will enroll healthy male and female participants aged ≥18 and ≤45 years at Screening.

Participants 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% and ≤50%African-American and/or West African adult participants in order to help assess potential population differences in safety, tolerability and PK in the primary clinical population. In addition, the Sponsor will attempt enroll ≥30% and ≤50% female subjects to ensure adequate representation of both sexes.

In the event a participant'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 participant can be considered eligible for the study. In the event a participant fails to meet the overall screening criteria, the participant may repeat the overall screening process once, and if the participant then meets all eligibility criteria, the participant will be considered eligible to enter the study.

4.1. Participant Inclusion Criteria

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

1. Is male or female, age 18 to 45 years, inclusive, at Screening.
2. Body mass index (BMI) between 18 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; participants 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/1.73 m^2 at Screening.
6. Females of childbearing potential must practice effective contraception per national regulatory guidelines for clinical trials from Screening (see Section 5.6.2), throughout the study, and for 60 days after the last dose of study drug.
7. Females must have a negative pregnancy test at Screening and within 24 hours prior to dosing of study drug; for post-menopausal participants, a blood sample will also be tested for estradiol and follicle stimulating hormone (FSH) to confirm post-menopausal status based on reference laboratory ranges for post-menopausal status. Surgically sterile females are eligible; however, proof via medical records will be required.
8. Males must agree to not donate sperm and to use condom and spermicide in combination with any of the means of contraception for their female partners detailed in Section 5.6.2 during sexual intercourse from the time of the first study drug administration and for

90 days following the last dose of study drug. 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 sun protection factor [SPF] 75 or greater sunscreen when outdoors) during the study treatment period.
10. Able to consume a standard meal (400-600 Calories) within 30 minutes.
11. Able to provide informed consent.
12. Willing and able to comply with this protocol and be available for the entire duration of the study.

4.2. Participant Exclusion Criteria

Participants 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. Prior exposure to ARN-75039.
4. 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.
5. 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 Day 15 Discharge visit.
6. Any female who is pregnant or breastfeeding, or any female who is planning to become pregnant during the study and safety follow-up period.
7. 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.
8. Inability to ingest all capsules of a multi-capsule dose within 5 minutes of ingestion of the first capsule.
9. Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening; participants with adequately treated HCV are eligible for enrollment.
10. Consumption of Seville oranges, grapefruit or grapefruit juice within 72 hours prior to Day 1 or during the study.
11. History of malignancy, except adequately treated basal cell carcinoma or in situ carcinoma of the uterine cervix.

12. Smoking cigarettes, cigars, cigarillos or E-cigarettes
13. Any reason or condition that, in the investigator's opinion, may compromise study participation, present a safety risk to the participant, 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 (including plasma) donation within 30 days before Screening.
16. Unwilling to consume a breakfast on study drug administration days.
17. History of:
    - Structural abnormality of the GI tract or a disease or history of a condition that can affect GI motility.
    - Inflammatory bowel disease (even if treated and currently in remission).
    - 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.
    - Chronic idiopathic diarrhea.
18. 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. Participant 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. History of chronic/generalized pruritus and/or skin rash of unknown origins.
23. Participants with diagnosed Type 1 or Type 2 diabetes, or with a fasting blood glucose value > 125 mg/dL during the screening period.

4.3. Participant Withdrawal Criteria

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

- Participant experiences any study drug-related Grade > 1 TEAE.

- Participant experiences any study drug-related Grade > 1 adverse event of special interest (AESI) as per Section 6.13.6.
- Participant withdraws consent.
- Physician decision
- Participant is non-compliant with study drug
- Participant becomes pregnant.
- Participant is unable to comply with the protocol requirements.
- Sponsor terminates the study.
- Study dosing cessation is mandated by a regulatory authority.

5. TREATMENT OF PARTICIPANTS

5.1. Description of Study Drug

5.1.1. Study Drug

ARN-75039 will be supplied to the clinical site in two formulations.

- Formulation A (reference) consists of 300 mg neat ARN-75039, which will be prepared by the onsite pharmacist during study conduct. The onsite pharmacist will dispense the specified weight of drug substance and will encapsulate the neat ARN-75039 in an HPMC capsule prior to oral dosing.
- Formulation B (test, tablet form) consists of 300 mg ARN-75039 with excipients in tablets, which is manufactured initially as a dry blend with 33.6% w/w ARN-75039 along with intragranular excipients including 33.6% Prosolv SMCC 90 LM (silicified microcrystalline cellulose), 1.0% Aerosil 200 (Fumed Silica), 2.4% Ac-Di-Sol SD-711 (Croscarmellose sodium) and 1% Magnesium stearate. Excipients do not have any pharmacological activity. The drug product was manufactured and prepared under current Good Manufacturing Practice (cGMP) regulations at PACE Life Sciences (Norristown, PA).

Both neat ARN-75039 in HPMC capsules and ARN-75039 with excipients in tablet form are administered orally.

5.2. Treatments Administered

This is an open label study.

As outlined in Figure 1, participants will be randomized into either Sequence 1 or Sequence 2. In Sequence 1, participants will receive 300 mg neat ARN-75039 in HPMC capsules during Period 1. After undergoing a 7-day washout period, participants in Sequence 1 will then receive 300 mg ARN-75039 with excipients in tablet form during Period 2.

In contrast, participants randomized into Sequence 2 will receive 300 mg ARN-75039 with excipients in tablet form during Period 1. After undergoing a 7-day washout period, participants in Sequence 2 will then receive 300 mg neat ARN-75039 in HPMC capsules during Period 2.

Study drug is to be administered in the fed state, with participants served a standard meal (approximately 400–600 Calories), which must be fully consumed within 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.

The reference drug product will be prepared by the onsite pharmacist or designee by dispensing the specified weight of drug substance and encapsulating it in an HPMC capsule prior to oral dosing. ARN-75039 drug substance and comparator drug product should be stored at 15–25°C. The comparator drug product (prototype 5) is manufactured initially as a dry blend with 33.6% w/w ARN-75039 along with extragranular excipients including 33.6% Prosolv SMCC 90 LM (silicified microcrystalline cellulose), 1.0% Aerosil 200 (Fumed Silica), 2.4% Ac-Di-Sol SD-711 (Croscarmellose sodium) and 1% Magnesium stearate. The material is dry blended for 10 minutes without magnesium stearate followed by 2 additional minutes of mixing with the

addition of magnesium stearate. The mix is added to Gerties Roller compactor whereby ribbons are generated with an average thickness of 1.75-1.92 mm. The ribbons are then granulated using a 20-mesh screen. To the dry granulated material additional intragranular excipients are added including 19.4% Prosolv, 2.4% Ac-Di-Sol SD-711 and 1.9% Magnesium stearate and the material added to Korsch XL100, 24 tablet press. After tablets are pressed, they are coated using 24" CompuLab Coater with 3.8% Opadry Titanium Free 276U110003 Green color and 1.0% Opadry II 85F19999 Clear Coat.

The PK of tablets having a highly similar formulation (Prototype 1 same excipients and dry blend step) was tested in dogs. The tablet formulation began with dry-blend including 40% ARN-75039, 40% Prosolv, 1.0% Aerosil 200, 2.5% Ac-Di-Sol SD-711 and 1.0% Magnesium stearate followed by extragranular excipients for tablet pressing of 12.0% Prosolv, 2.5% Ac-Di-Sol SD-711 and 1% Magnesium stearate. The formulation was changed to prototype 5 because picking was observed during tablet pressing of prototype 1. A 100 mg tablet of protype 1 formulation and a prototype 5 formulation were orally delivered to dogs and compared to HPMC capsules filled with 100 mg neat ARN-75039. Mean PK values are presented in Table 2.

Table 2: Mean Pharmacokinetics of ARN-75039 100 mg Prototype 1 and Prototype 5 Tablets and HPMC Capsules

Oral Dose	C_{max} ng/mL	T_{max} (h)	AUC_{0-24} (ng/mL*hr)	C_{min} 24 hr ng/mL (µM)	Clearance (mL/min/kg)	Vd (L/kg)
100 mg API Neat in HPMC capsule	4518	5	45453	369.1 (0.89)	4	4
100 mg tablet P1	5105	2	39211	335.6 (0.81)	4	7
100 mg tablet P5	5346	4	42542	399 (0.96)	5	-

Abbreviations: API = active pharmaceutical ingredient; HPMC = hydroxypropyl methylcellulose

Prototype 5 stability after one month at both long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability is presented in Table 3.

Table 3: One-Month Stability of Prototype 5 Tablets

Time Point		Long-term Stability (25°C/60%RH)	Accelerated Stability (40°C/75%RH)	Specification
Initial	--	100%		90–110% of Label Claim
1 Month	--	99.5%	100%	
Related Substances				
Initial	RRT 0.66	0.05%		• Report all impurities ≥ 0.05% area • Individual Unspecified Degradation Impurities NMT 0.5% area • Total Degradation Impurities NMT 5% area
	iPrBA	0.06%[1]		
	Total Impurities	0.0%[2]		
1 Month	RRT 0.53	0.05%	0.05%	--
	RRT 0.94	0.05%	<LOQ	--
	Total Impurities	0.1%	0.1%	--

Abbreviations: LOQ = limit of quantitation; NMT = not more than; RH = relative humidity; RRT = relative retention time

[1] iPrBA is a process impurity not a degradation impurity. Process impurities are reported but excluded from total degradation impurity calculations.

[2] Individual degradation impurities are reported to two decimal places. Total impurities are reported to one decimal place. RRT 0.66 rounds to 0.05% when reported to two decimal places but 0.0% when reported to one decimal place.

5.3. Selection and Timing of Dose for Each Participant

Study drug is to be administered in the fed state, with participants served a standard meal (approximately 400–600 Calories), which must be fully consumed within 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.

5.4. Methods of Assigning Participants to Treatment Groups

To eliminate potential bias, participants will be randomly assigned to either Sequence 1 or Sequence 2. The study site will utilize the randomization result generated to administer the appropriate study drug formulation to participants in accordance with the Study Schema (Figure 1) and the Schedule of Assessments (Table 1).

5.5. Individual and Study Stopping Rules

5.5.1. Individual Stopping Rules

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

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

5.5.2. Study Stopping Rules

The study may be stopped at the discretion of the sponsor or for any reason specified in Section 3.5 Criteria for Study Termination. In all cases, all necessary measures will be taken to ensure appropriate safety follow-up of all participants in the trial.

5.6. Concomitant Medications

5.6.1. Prohibited Medications

The following concomitant therapies are prohibited:

- Use of any prescription or OTC medications, including 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 (also known as paracetamol) (not exceeding 2 grams/day) within 7 days prior to study drug administration and through the Day 15 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 Day 15 visit.

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.

5.6.2. Contraception

Individuals of reproductive potential who are (hetero) sexually active must be willing to use effective contraception from Screening through 60 days after the Day 15 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: Males must agree to not donate sperm and to use condom and spermicide in combination with any of the above means of contraception for their female partners during sexual intercourse from the time of the first study drug administration and for 90 days following the last dose of study drug.
- 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.

5.6.3. Restrictions

Participants must adhere to the following restrictions during study participation:

- Smokers of cigarettes, cigars, cigarillos, or E-cigarettes.
- 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 Day 15 visit.
- No strenuous activity from 48 hours prior to Day -1 through the last PK sample collection time point.
- No blood product (including plasma) donation within 30 days before Screening through Day 15, 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 Study Days 1 through 15.

5.7. 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 participant'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 International Council for Harmonisation (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.

5.8. 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. ARN-75039 will be supplied to the clinical site as both a neat drug substance and with excipients in tablet formulation. The shipment, packaging, and encapsulation of both formulations of the drug substance and the labeling of the study drug prior to administration to participants are detailed in the Pharmacy Manual.

5.9. Investigational Product Retention at Study Site

It is the responsibility of the Investigator to ensure that all 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 drug substance, encapsulated study drug and tablet drug substance. 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 participant 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 participant enters the Screening Period.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants 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 participant and signed and dated informed consent is to be obtained before any study specific procedures are performed. A copy of the signed and dated ICF should be provided to the participant.

6.2. Medical History

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

A recent medical history will be obtained on Day -1 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 participant's recent medication use.

6.3. Physical Examination

A complete physical examination will be conducted at the time points designated in the schedule of assessments (SOA) (Table 1). 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 participant complaints or changes from baseline as clinically indicated.
- Symptom-directed physical examination should be completed 24 hours post-dose.

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

Electrocardiograms (ECGs) will be performed at screening, admission, pre-dose, on dosing days Day 1 in each period (3–6h post-dose, approximate C_{max}), and on Day 15 or at the ET visit with all measurements taken within 5 minutes apart. Triplicate ECGs will be measured at pre-dose, and post dose 1hr, 3hr, 6hr, 8hr, 24hr, 48hr, and 72hr post dose (for both doses) triplicates

measurement will be taken within 5 minutes apart. Subjects should be at rest for 10 minutes prior to ECG. For participants that withdraw or are terminated early from the study, ECG will be performed at the ET visit. ECG time points are indicated in the SOA (Table 1). The date and time of each ECG and its results will be documented in the source documents and transcribed into the eCRF.

6.5. Alcohol and Drug Screening

Participants will undergo urine drug and breath alcohol screening to confirm the absence of alcohol or substances of abuse (including amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids) at Screening, upon admission to the unit, 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 4.

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 participant to be eligible for the study; however, participants with adequately treated HCV (HCV ribonucleic acid negative) are eligible for enrollment.

6.7. Vital Signs

Vital signs, including systolic (SBP) and diastolic blood pressure (DBP), heart rate, 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 1). Vital signs (except for height and weight) will be monitored periodically during and following study drug administration. The investigator may repeat the vital signs if deemed appropriate.

Participant must be in a rested seated or supine position and in calm state for at least 3 minutes before vital signs are collected. When possible, blood pressure should be taken in the arm not being used for blood sample collections 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 at the discretion of the investigator or designee.

6.8. Safety Laboratory and Pregnancy Testing

Clinical laboratory testing will be performed at the time points designated in the SOA (Table 1) Samples for safety laboratory testing are to be collected following a minimum 8-hour fast. Participants 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 women, serum human chorionic gonadotropin pregnancy test will be performed at Screening, urine test at the time of admission to the clinic (Day -1), and at Day 15 Discharge or at Early Termination. Laboratory tests are listed in Table 4.

Table 4: Clinical Laboratory Tests

<table>
<tr>
<td colspan="2">Hematology:
• Hematocrit
• Hemoglobin
• Platelet count
• RBC count
• WBC count – with differential</td>
<td rowspan="4">Serum Chemistry:
• Glucose
• BUN
• Creatinine
• Total bilirubin
• AST
• ALT
• GGT
• Alkaline phosphatase
• Creatine kinase
• Total protein
• Lactate dehydrogenase
• Direct bilirubin
• Total bilirubin
• Sodium
• Potassium
• Total CO_2
• Chloride
• Calcium
• Inorganic phosphate
• Magnesium
• eGFR</td>
</tr>
<tr>
<td colspan="2">Coagulation:
• PT/INR
• PTT</td>
</tr>
<tr>
<td colspan="2"><u>Urinalysis</u>:
• Bilirubin
• pH
• Specific gravity
• Protein
• Leukocytes
• Urobilinogen
• Glucose
• Nitrates
• Ketones
• Blood
• Microscopic urine analysis</td>
</tr>
<tr>
<td colspan="2"><u>Urine Drug Screen:</u>
• Amphetamines
• Barbiturates
• Opiates
• Benzodiazepines
• Cocaine metabolites
• Cannabinoids</td>
</tr>
<tr>
<td colspan="2">Pregnancy Testing:
• Serum hCG – at Screening
• Urine hCG – at the time of study center admission and Day 15 Discharge or ET</td>
<td rowspan="2">Post-Menopausal Status Testing:
• FSH
• Estradiol</td>
</tr>
<tr>
<td colspan="2">Alcohol Screening:
• Breath alcohol test</td>
</tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; eGFR = estimated glomerular filtration rate; 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.

6.8.1. Sample Collection, Storage, and Shipping

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 laboratory sample handling, storage, and shipping are provided in the Laboratory Manual.

6.9. Dispensing Study Drug

Following Screening and reconfirmation of eligibility at the time of clinic admission, participants will be randomly assigned to a treatment sequence according to the study center's SOPs. Using the randomization schedule, the onsite pharmacist will prepare and deliver the appropriate study drug to the study center for dosing.

6.10. Pharmacokinetics

Fifteen venous blood samples will be withdrawn via an indwelling cannula or by venipuncture at regular time intervals. The exact date and time of PK sample collection is to be documented in the eCRF. Blood samples will be collected prior to and following administration of the single oral dose of neat ARN-75039 in HPMC capsules or ARN-75039 with excipients in tablet form at according to the timepoints listed in the SOA (Table 1). On Day 15 or at ET, the PK blood sample at approximately the same time as the dose of study drug was administered.

6.11. Discharge from the Study Center

Participants are to be discharged from the study center as indicated in the SOA (Table 1).

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

6.12. Adverse and Serious Adverse Events

6.12.1. Definition of Adverse Events

6.12.1.1. 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. Any reported AEs prior to first study drug administration will be documented within the participant's medical history.

6.12.1.2. 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 participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

- 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 participant 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 participant hospitalization, or the development of drug dependency or drug abuse.

All SAEs that occur after the start of study drug administration through the end of study (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.

6.12.1.3. 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.

6.12.1.4. 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.

6.12.1.5. Treatment-Emergent Adverse Events (TEAE)

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.

6.12.2. 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 participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant.
  - 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.

6.12.3. 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:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: 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 6.13.1.2. An AE of severe intensity may not be considered serious.

6.12.4. Recording Adverse Events

AEs spontaneously reported by the 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 subject to discontinue the study.

6.12.5. Pregnancy

Should a pregnancy occur in a female participant or the partner of a male participant, 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.

6.12.6. Adverse Events of Special Interest (AESI)

All AEs and SAEs that occur during the study will be reported and investigated. However, because of observations of tachycardia, early 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 elevated heart rate, GI and skin-related signs and symptoms.

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 6.13.3 and relationship to study drug similarly as for SAEs (Section 6.13.2).

Any AESI deemed as related (e.g., definitely, probably, or possibly), greater than grade 1 or severe (if not included in the NCI CTCAE) may require discontinuation of dosing of ARN-75039 (and follow-up until resolution) per the discretion of the Investigator and Sponsor Medical Monitor.

6.12.7. Reporting Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 6.13.1.2). 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 participant 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 participant report, relevant source document request and review, and SAE report entry within the eCRF. (Participant 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
- Participant 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. The study site is responsible for notifying its IRB of these additional SAEs.

6.13. Concomitant Medication Assessments

All prescription and OTC medications, herbals, and supplements taken by participants during the study (i.e., from signing the ICF through the Day 15 visit) must be documented on the source document and transcribed into the eCRF.

7. STATISTICS

7.1. General Considerations

The sample size has been selected in accordance with standard designs for Phase 1 assessments of PK, safety, and tolerability and is sufficient to meet the objectives of the study.

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

Reasons for study discontinuation will be listed on a per-participant 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 participants who receive any amount of ARN-75039 in either formulation, and have sufficient data to be included in the PK analysis post-dose concentration-time data to determine at least 1 PK parameter.

All safety analyses will be based on the Safety Population, which includes all participants 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 treatment sequence and overall.

7.6. Extent of Exposure

A by-participant 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, 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 system organ class and preferred term by treatment. Additionally, TEAEs and AESIs will be presented by treatment for each relationship and 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 provided in a data listing.

The overall interpretation of the ECG result will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) for each day, by treatment. Descriptive statistics will be presented for the ECG measurements and change from baseline collected at each day by treatment.

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

For each vital sign measurement and changes from baseline at each time point, descriptive statistics will be presented by treatment.

7.9. Pharmacokinetic Analyses

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

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

C_{max}	maximum plasma concentration
t_{max}	time of maximum plasma concentration
λ_z	terminal-phase rate constant
$t_{½}$	elimination half-life
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours post-dosing
AUC_{0-t}	area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
CL/F	apparent clearance
MRT	mean residence time
V_z/F	apparent volume of distribution

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

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

Additional details regarding PK analyses will be documented in a formal 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 subject'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 subject (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 participant 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 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 subjects 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 participants 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 participants, 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 subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’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 subject.

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.

11. LIST OF REFERENCES

Asogun DA, Gunther S, Akpede GO, Ihekweazu C, Zumla A. Lassa Fever: Epidemiology, Clinical Features, Diagnosis, Management and Prevention. *Infect Dis Clin North Am*. 2019;33(4):933-51. doi: 10.1016/j.idc.2019.08.002.

Balogun OO, Akande OW, Hamer DH. Lassa Fever: An Evolving Emergency in West Africa. *Am J Trop Med Hyg*. 2020;104(2):466-73. doi: 10.4269/ajtmh.20-0487.

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