CLINICAL STUDY PROTOCOL: ARN-75039-101

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, 2-Part (Single-Ascending Dose and Multiple-Ascending Dose) Study to Assess the Safety, Tolerability, and Pharmacokinetics of ARN-75039 When Administered by the Oral Route in Healthy Adult Subjects

Statistical Analysis Plan

Version 2.0: 06 June 2024

CONFIDENTIAL AND PROPRIETARY INFORMATION

Statistical Analysis Plan Signature Page

Study Title:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, 2-Part (Single-Ascending Dose and Multiple-Ascending Dose) Study to Assess the Safety, Tolerability, and Pharmacokinetics of ARN-75039 When Administered by the Oral Route in Healthy Adult Subjects
Investigational Product:	ARN-75039
Sponsor:	Arisan Therapeutics, Inc. 5825 Avenida Encinas, Suite 101 Carlsbad, CA 92008 USA
Protocol Number:	ARN-75039-101
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Statistical Analysis Plan Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Main Changes and Rationale**	**Date**
Original, Version 1.0	–	16 May 2023
Version 2.0	Updates to the dose regimens of ARN-75039 as well as number of cohorts in the Part 2 MAD study. For Part 2 only, added summary tables for adverse events of special interest, the colonic transit test, and clinical questionnaire results.	06 June 2024

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LIST OF ABBREVIATIONS

β	beta
λ_z	terminal elimination rate constant
AE	adverse event
ANOVA	analysis of variance
AR_{AUC}	accumulation ratio based on AUC
AR_{Cmax}	accumulation ratio based on C_{max}
AUC	area under the concentration-time curve
$AUC_{0-\tau}$	AUC from time 0 to the end of dosing interval
$AUC_{0-\infty}$	AUC from time 0 extrapolated to infinity
AUC_{0-10h}	AUC from time 0 to 10 hours following the morning dose
AUC_{0-12h}	AUC from time 0 to 12 hours
AUC_{0-24h}	AUC from time 0 to 24 hours
AUC_{0-t}	AUC from time 0 to time of the last quantifiable concentration
AUC_{ext}	percentage of $AUC_{0-\infty}$ due to extrapolation from the time of the last quantifiable concentration to infinity
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
C_{6h}	concentration at 6 hours
CI	confidence interval
C_{last}	last quantifiable plasma concentration
CL/F	apparent clearance after extravascular administration
CL_{ss}/F	apparent clearance after multiple extravascular administrations
C_{max}	maximum observed plasma concentration
$C_{max0-10h}$	maximum observed plasma concentration from 0 to 10 hours following the morning dose
$C_{max0-24h}$	maximum observed plasma concentration from 0 to 24 hours following the morning dose
C_{min}	minimum observed plasma concentration
$C_{min4-12h}$	lowest concentration from 4 to 12 hours following the first dose on Day 1.
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CSR	clinical study report

CTCAE	common terminology criteria for adverse events
C_{trough}	concentration at the end of the dosing interval
$DNAUC_{0\text{-}10h}$	dose-normalized $AUC_{0\text{-}10h}$
$DNAUC_{0\text{-}\tau}$	dose-normalized $AUC_{0\text{-}\tau}$
$DNAUC_{0\text{-}\infty}$	dose-normalized $AUC_{0\text{-}\infty}$
$DNAUC_{0\text{-}t}$	dose-normalized $AUC_{0\text{-}t}$
DNC_{max}	dose-normalized C_{max}
$DNC_{max0\text{-}10h}$	dose-normalized $C_{max0\text{-}10h}$
CV%	percent coefficient of variation
ECG	electrocardiogram
EOS	end-of-study
FDA	Food and Drug Administration
GLSMR	geometric least-squares mean ratio
ln	natural logarithm
LS	least-squares
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NR	no result
NS	not seen
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2_{adj}	adjusted coefficient of determination
RP2D	recommended Phase 2 dose
SAD	single ascending dose
SAP	statistical analysis plan
SMC	Safety Monitoring Committee
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{last}	time to C_{last}
T_{max}	time to maximum observed concentration

$T_{max0\text{-}10h}$	time to $C_{max0\text{-}10h}$
$T_{max0\text{-}24h}$	time to $C_{max0\text{-}24h}$
T_{min}	time to minimum observed concentration
$T_{min4\text{-}12h}$	time to $C_{min4\text{-}12h}$
V_z/F	volume of distribution after extravascular administration
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used for the analysis and summarization of pharmacokinetic (PK) and safety data from Protocol ARN-75039-101. Details of all planned statistical analyses provided in the current SAP will supersede those described in the protocol.

The SAP will be finalized before database lock and unblinding. Any changes made after finalization of the SAP will be documented in the clinical study report (CSR). Related documents are the study protocol and electronic case report forms.

The SAP V1.0 was finalized before Part 2 of the study was initiated. The protocol V4.2 necessitated an amendment to the SAP as V2.0.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single and multiple doses of ARN-75039 when administered by the oral route at escalating dose levels in healthy adult subjects.	• Type and frequency of treatment-emergent adverse events (TEAEs) • Type and frequency of treatment-emergent serious adverse events (TESAEs) • Type and frequency of study drug-related >Grade 1 TEAEs • Type and frequency of changes in clinical laboratory values, electrocardiograms (ECGs), colonic transit time (biomarker), physical examinations, and vital signs
Secondary	
To assess the pharmacokinetics of single and multiple doses of ARN-75039 when administered by the oral route. To assess the effect of food on the PK of single oral administrations of ARN-75039. To determine the recommended Phase 2 dose (RP2D) and regimen of ARN-75039 capsules.	• PK parameters of ARN-75039 capsules, as appropriate for single or multiple dose administration and study design, including but not limited to: – Area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{0-t}) – Appropriate partial AUCs: AUC from time 0 to the end of the dosing interval ($AUC_{0-\tau}$) or alternative partial AUCs as appropriate to the dosing regimen (eg, AUC_{0-12} for twice daily [BID], if applicable, and AUC_{0-24} for once daily [QD]) to properly address the study objectives – AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$) – Maximum observed plasma concentration (C_{max}) – Time to reach C_{max} (T_{max}) – Terminal elimination half-life ($t_{1/2}$) – Apparent clearance after extravascular administration (CL/F)

	– Volume of distribution after extravascular administration (V_z/F) • RP2D and regimen of ARN-75039 capsules[a]

[a]RP2D and regimen of ARN-75039 capsules will be determined by Arisan Therapeutics, Inc.

3 STUDY DESIGN

3.1 Number of Subjects

The study will enroll approximately 82 subjects (up to 98 subjects), 18 to 55 years of age in general good health, who satisfy all of the inclusion criteria and none of the exclusion criteria and have satisfied all screening evaluations before enrollment in the study. In Part 1 (single ascending dose [SAD]), 42 subjects are planned to be enrolled across 5 cohorts with an optional additional cohort of 8 subjects. In Part 2 (multiple ascending dose [MAD]), 40 subjects are planned to be enrolled across 5 cohorts with an optional additional cohort of 8 subjects.

3.2 Sample Size Considerations

No formal sample size calculations have been performed based on statistical considerations. This study utilizes the sample size that is commonly employed in early clinical pharmacology studies, in order to assess safety, tolerability, and PK of escalating single and multiple doses. Subjects who are withdrawn or discontinued from the study for a reason other than toxicity during the treatment period may be replaced.

3.3 Study Design

This is a Phase 1, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and PK of escalating single and multiple doses of ARN-75039 when administered by the oral route in healthy adult subjects. Six SAD cohorts and approximately 6 MAD cohorts, with approximately 8 subjects per cohort (with the exception of 1 SAD cohort to evaluate the effect of food with approximately 10 subjects), will be enrolled to receive study drug by the oral route in the fed state. Within each cohort of 8 subjects, the first 2 subjects will be randomly assigned in a 1:1 ratio to receive ARN-75039 capsules or placebo. After a review by the medical monitor of the first 3 days of blinded safety for these subjects, an additional 6 subjects will be randomly assigned in a 5:1 (active: placebo) ratio. Within the food effect cohort of 10 subjects, the first 2 subjects will be randomly assigned in a 1:1 ratio to receive ARN-75039 capsules or placebo. After a review by the medical monitor of the first 3 days of blinded safety for these subjects, an additional 8 subjects will be randomly assigned in a 7:1 (active: placebo) ratio. An optional cohort of approximately 8 subjects may be added to either the SAD or MAD portions of the study. The study cohorts are described in Table 1

Table 1: Distribution of Subjects in Study Parts and Cohorts

Study Part	Cohort	Meal	Dose	Active Subjects (Number of Subjects)	Matching Placebo (Number of Subjects)
1: SAD[1]	1	Fed	30 mg	6	2
	2	Fed	100 mg	6	2
	3	Fed/Fasted	300 mg	8	2
	4	Fed	600 mg	6	2
	5	Fed	1200 mg	6	2
	6	Fed	2000 mg (up to 2400 mg planned)	6	2
2: MAD[2]	7	Fed	Day 1: 36 and 24 mg doses Day 2: 24 mg BID Days 3-10: 12 mg BID	6	2
	8	Fed	Day 1: 75 and 50 mg doses Day 2: 50 mg BID Days 3-10: 25 mg BID	6	2
	9	Fed	Day 1: 180 and 120 mg doses Day 2: 120 mg BID Days 3-10: 60 mg BID	6	2
	10	Fed	Day 1: 240 and 160 mg doses Day 2: 160 mg BID Days 3-10: 80 mg BID	6	2
	11	Fed	Day 1: 300 and 200 mg doses Day 2: 200 mg BID Days 3-10: 100 mg BID	6	2
	12 (optional)	Fed	Day 1: ≤375 and 250 mg doses Day 2: 250 mg BID Days 3-10: 125 mg BID	6	2

Abbreviations: BID, twice daily; MAD, multiple ascending dose; SAD, single ascending dose.

Note: BID doses will be administered approximately 10 hours apart.

1 As conducted. Optional cohorts were added for Part 1 (SAD) to include a food effect cohort (Cohort 3). Dose escalation up to 2400 mg was planned; in Cohort 6, a dose of 2000 mg was administered.

2 As planned. The Sponsor will assess and potentially adjust the planned doses and regimens for Part 2 (MAD) based on all available safety and PK data from Part 1 (SAD) and Part 2 (MAD). Optional MAD cohort(s) may be added.

The planned starting dose level in the SAD cohort is 30 mg orally, with escalation to doses of 100, 300, 600, and 1200 mg planned. An optional cohort dosed up to 2400 mg may be included depending on safety and PK data from earlier SAD cohorts; an actual dose of 2000 mg was administered in an optional cohort (Cohort 6).

In Part 2 (MAD), dose regimens include twice daily (BID) dosing and have been designed

generally as follows: On Day 1 an initial 3× (relative to maintenance dose) loading dose will be administered followed by a 2× dose. On Day 2, 2× (relative to maintenance dose) BID dosing will be administered. On Days 3–10, BID administration of a 1× maintenance dose will be provided. The planned dose regimens in cohorts 7–12 are provided in the table above, including an optional cohort with doses of ≤ 375 mg and 250 mg on Day 1, 250 mg BID on Day 2, and 125 mg BID on Days 3–10. Doses will be administered approximately 10 hours apart. The dose levels and dosing intervals in the MAD cohorts have been determined based on the safety and PK of ARN-75039 demonstrated in the SAD part of the study along with non-clinical general toxicity findings observed in rats and dogs, with the objective of determining the RP2D.

Additional optional SAD and/or MAD cohorts may be added to further evaluate dosing for safety and PK for future studies and/or relative bioavailability and relative bioequivalence of an alternative formulation/drug product, at the discretion of the sponsor in consultation with the Safety Monitoring Committee (SMC).

An overview of each study part follows:

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

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

- **Part 2 MAD:** The MAD part of the study will be initiated after the safety and PK data from the SAD part of the study have been reviewed by the Food and Drug Administration (FDA) and the sponsor and FDA have determined that it is safe to proceed. The MAD part of the study will utilize BID oral doses of ARN-75039 for a total of 10 days for each subject, with doses administered approximately 10 hours apart. The proposed doses and dose regimen have been determined based on the safety and PK results from the SAD part of the study and safety margins (ranging from 50- to 8-fold) of predicted $AUC_{0\text{-}24}$ for the proposed dose regimen and mean (combined sex) $AUC_{0\text{-}24}$ of the rat NOAEL at 50 mg/kg. Two sentinel subjects per cohort will be randomly assigned (1 active and 1 placebo) and may be dosed on the same day; subsequent subjects in that cohort may be dosed after an 8-day safety observation period during continuous oral dosing, with the approval of the medical monitor. Dose escalation to the next cohort may occur after review by the SMC of blinded safety and available PK data from all subjects in all available cohorts through Day 8. Up to 5 MAD

cohorts are planned, comprising a total of approximately 40 subjects to be administered study drug in Part 2 of the study (30 assigned to ARN-75039 and 10 assigned to placebo). One additional cohort of 8 subjects is optional.

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

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

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

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

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

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

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

  Subjects will return to the CRU for follow-up evaluations according to the schedule of assessments (Part 1 SAD: Table 2, Part 2 MAD: Table 3, Food Effect: Table 4) during the Treatment Period.

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

- **Safety Follow-up Period:** The Safety Follow-up Period will have a duration of 14 days for the SAD part of the study and 28 days for the MAD part of the study, culminating with an

End-of-study (EOS) Visit. For subjects who withdraw from the study prematurely, the EOS visit is to be conducted within 7 days after the last study drug dose.

With the exception of the fasted portion of the food effect cohort, study drug will be administered in the fed state, with subjects served a meal 30 minutes before 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 second dose of the food effect cohort will be administered to subjects at the CRU after an overnight fast of at least 10 hours. Water will be allowed for up to 2 hours before dosing, then restricted until 2 hours postdose, with the exception of water taken (up to 240 mL) with capsule administration.

Study duration for subjects in Part 1 is approximately 6 weeks, with the food effect cohort being 9 weeks. Duration for subjects in Part 2 is approximately 10 weeks.

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

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

If a subject has a study drug-related >Grade 1 TEAE during the Treatment Period, study drug dosing will be discontinued for that subject. Subjects experiencing a study drug-related >Grade 1 TEAE will be asked to remain in the study and complete the study visits through the EOS visit. These subjects will not be replaced.

If a subject terminates early for a reason other than a toxicity during the Treatment Period, the subject may be replaced. Study drug dose level modifications or dosing administration deviations outside the protocol-specified windows are not permitted during the Treatment Period.

The schedule of assessments for each part of the study are shown in Table 2 (Part 1, SAD), Table 3 (Part 2, MAD), and Table 4 (Food Effect).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Procedure	Screening (Days -35 to -1)	Study Day[a]										
		-1	1	2	3-7	8	9	10	11	17 ± 2 D	25 ± 2 D[p]	(EOS)[b] 39 ± 2 D
SITZMARKS® Test	X			X[l]	X[m]							
Admittance to study center		X										
Food Consumption Measurement		X	X	X	X	X	X	X				
Randomization			X									
Pharmacokinetics (plasma)[k]			X	X		X		X		X		X
Study drug administration[a]			X	X	X	X	X	X				
Clinical Questionnaire	X[q]	X[q]	X	X	X	X	X	X	X	X	X	X
Discharge from study center									X			

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

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

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

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

d Vital signs include systolic (SBP) and diastolic blood pressure (DBP), pulse, respiration rate, and oral temperature. At the Screening Visit, height, weight and BMI will be measured. At subsequent visits, the weight and BMI will be measured once per day. Vital signs will be monitored periodically during and following study drug administration. Subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. The following vital sign collection time points and windows are applicable during the confinement period for the MAD part of the study: For the first dose on Day 1: within 60 min pre-dose, 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), 4 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), and 24 hr (can be combined with pre-dose for the following dose day, where applicable) (24 hour/predose ±30 min). For the second dose on Day 1, within 60 min pre-dose, 15 min (±10 min), 30 min (±10 min), 60 min (±10 min), 2 hr (±10 min), and 4 hr (±10 min). For Days 2-10, vital signs will be measured only one hour post-dose for each dose (e.g., AM and PM doses). On Day 11, Day 17, and the EOS visit (or early termination), one exit vital signs measurement will be taken.

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

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

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

h Triplicate ECGs will be extracted from Holter monitor 6 hour post-dose (assumed C_{max}) with each measurement taken within 5 minutes apart. Subjects should be supine for 10 minutes prior to ECG. Thereafter, in subsequent cohorts, the ECG is to be performed at the time point coincident with C_{max}, as determined in Cohort 7. Continuous 12-lead ECG data will be collected from pre-dose until at least 6 hours post, this data will be collected and stored.

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

Procedure	Screening (Days -35 to -1)	Study Day[a]										
		-1	1	2	3-7	8	9	10	11	17 ± 2 D	25 ± 2 D[p]	(EOS)[b] 39 ± 2 D

j Serology includes HbsAg, anti-HCV Ab, anti-HIV Ab.
k PK assessments should be performed on Day 1 and Day 10 predose, and at 30 minutes, then 1, 2, 4, 6, 8, 10 (prior to second daily dose), 12, 14, and 24 hours after initial morning dose (pre-dose sample). Predose (relative to morning dose) samples should be collected on Days 3 and 8. Separately, 6 hour post dose (relative to morning dose) samples should be collected on Days 2 and 8. A PK sample should also be collected on Days 17 and 39 (EOS). The PK collection windows are located in Section 6.15.
l Day 2 administration of capsule with radiopaque markers between BID doses of study drug (i.e., approximately 5 hours after the morning dose of study drug on Day 2).
m Day 7 abdominal X-ray to read number of radiopaque markers not expelled.
n On Day 5 only.
o Insulin sampled Day -1, 5, 10. Samples must be collected following a minimum 8 hour fast.
p Blood glucose only
q Screening clinical questionnaire (eligibility and baseline)
r The ophthalmologic examination may be done +/- 1 day

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.4 Unblinding Procedures

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

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

In the event of an emergency, the investigator can contact the medical monitor. If it is determined that unblinding is necessary in order to treat the emergency, after consulting the medical monitor/sponsor, if possible, the investigator may be unblinded according to the CRU's standard operating procedures.

A statistician, pharmacokineticist, and peer PK reviewer at Spaulding Clinical will be unblinded in order to analyze and review the PK data between cohorts and for the interim PK analysis, as described in Section 4.4.

The study blind will be maintained for all other personnel until the database is locked. Once the database is locked, a blind-break request form will be signed by a sponsor representative, the study statistician, and the data manager. Subsequently, the randomization schedule will be provided to unblind the study.

4 GENERAL STUDY CONSIDERATIONS

4.1 Statistical Considerations

All analyses described in this SAP are considered a priori analyses in that they have been defined before breaking the blind. All other analyses, if any, designed subsequent to locking the database and breaking the blind will be considered post hoc analyses and exploratory methodology will be applied. All post hoc analyses performed after locking the database and breaking the blind will be identified and documented in the CSR.

All statistical tests will be 2-sided with $\alpha = 0.05$, unless otherwise stated. Descriptive statistics for continuous variables will include number of subjects/observations, mean, median, SD, minimum, and maximum, unless otherwise stated. For PK summaries, the percent coefficient of variation (CV%), geometric mean, and geometric CV%, will also be presented. Descriptive statistics for categorical variables will consist of frequency counts and percentages.

Summary statistics will be presented as follows: The number of subjects/observations will be presented without any decimal places, minimum and maximum with the same precision as the reported values, arithmetic and geometric means, and median to 1 more level of precision than the reported values, SD to 2 more levels of precision than the reported values, CV% and geometric CV% to 1 decimal place. Percentages will be reported to 1 decimal place. In the event that the reported percentage is 100%, no decimal place will be presented. The precision to be used for inferential statistics is detailed in Section 7.3 and Section 7.4.

All statistical analyses will be conducted using SAS® Version 9.4 (SAS Institute Inc., Cary, NC) or later.

For the purposes of summarization, placebo subjects will be pooled across single- and multiple-dose cohorts, separately. For the food effect cohort, placebo subject data associated with the study drug administration under fasted conditions will be summarized separately. Summaries of Part 1 SAD and Part 2 MAD will be reported separately.

4.2 Handling of Missing Data

Data that are excluded from the descriptive or inferential analyses will be included in the data listings. This will include measurements from excluded subjects or measurements from unscheduled visits/collections, except as described in the individual summary sections where unscheduled data may be included when presenting worst value or maximum postbaseline summaries.

In calculation of the plasma concentration summaries and displays in figures, values that are below the limit of quantification (BLQ) will be set to zero unless the BLQ value is deemed implausible (eg, between 2 quantifiable concentrations), in which case it will be set to missing. However, they will be presented as BLQ in data listings. If all concentrations at a given time point are BLQ, the mean will be presented as zero and the SD, CV%, geometric mean, and geometric CV% will be reported as not applicable. If a mean concentration is BLQ it will be flagged in the summary table.

For the calculation of PK parameters, BLQ values will be treated as follows:

- In samples collected before study drug administration or before the first quantifiable concentration, BLQ values will be set to zero.
- In samples occurring after the first quantifiable concentration, BLQ values will be set to missing. If 2 BLQ values occur in succession any time after C_{max} has been attained, the profile will be deemed to have terminated at the first BLQ value and any subsequent quantifiable concentrations will be treated as missing and excluded from the PK analysis, unless they are considered to be a true characteristic of the profile of ARN-75039.

Concentration data reported as missing (eg, no result [NR]) will not be imputed, with the exception of predose plasma concentrations that are used for the calculation of PK parameters, which will be handled as follows:

- Part 1 (SAD), Food Effect Cohort, and Day 1 for Part 2 (MAD): set to zero
- Day 10 morning dose for Part 2 (MAD): set to the concentration at 24 hours after the morning dose

All PK analyses will use actual sampling times. If actual times are missing, nominal times may be used, if deemed appropriate, and will be noted in the appropriate data listing.

Missing data will not be imputed (except as stated above).

4.3 Key Definitions

Baseline value is defined as the last available value, whether scheduled or unscheduled, collected before the first study drug administration, unless otherwise specified. For the food effect cohort, baseline for a specified treatment period (fed/fasted) is defined as the last available value, whether scheduled or unscheduled, collected before the first study drug administration in each treatment period (fed/fasted).

Relative study day is defined as the number of days from the first dose date and will be presented in all data listings where a complete date is presented. The first dose day is Day 1. The previous day is Day –1. There is no Day 0.

4.4 Interim Analyses

SAD By-Cohort PK Analyses

Raw concentration data provided by the bioanalytical laboratory will be de-identified and provided to the sponsor for Part 1 (SAD). The data will be reviewed by an unblinded statistician and pharmacokineticist at Spaulding Clinical before providing to the sponsor to confirm there is no potential for unblinding. Any data which has the potential to unblind will not be sent.

The unblinded Spaulding Clinical pharmacokineticist will conduct PK analyses after each SAD cohort (including the food effect cohort) and will provide blinded summaries of PK results to the Sponsor. The by-cohort PK analyses to be performed are outlined in the Interim Pharmacokinetic

Analysis Plan. Summaries will be provided in lieu of individual data to avoid potential to unblind, and descriptive statistics (or other data) presented may be limited in order to maintain the blind (as applicable).

The estimation of steady state exposure and dose proportionality analyses to be provided with the interim PK analysis (ie, Cohort 6) were also included with the by-cohort analyses for Cohorts 4 and 5.

Interim Analysis

Part 1 SAD

A blinded interim analysis of safety and PK data from Part 1 (SAD), will be conducted to support regulatory submission and determine the dosing regimen for Part 2 (MAD). The interim safety analysis will be based on data that has been databased prior to the generation of the interim report.

Disposition, demographic and baseline characteristics, and safety outputs to be generated for the interim analysis will have the same format as the final outputs for the CSR, with the exception of being presented by cohort instead of treatment with no placebo due to the blinded nature of the analysis. The blind will be maintained for the disposition, demographic and baseline characteristics, and safety outputs by presenting all outputs by cohort instead of treatment and no listings by treatment will be provided. Outputs to be provided for the interim analysis are indicated within the list of tables, listings, and figures in Appendix A.

An interim PK report will be provided, with blinded summaries of the available PK results, as outlined in the Interim Pharmacokinetic Analysis Plan. In addition to the summaries described, a listing of individual concentration data for subjects who received active treatment will be provided. Presentation of individual data and descriptive statistics may be limited in order to maintain the blind (as applicable).

Part 2 MAD

An interim analysis of safety (blinded) and PK data from Cohorts 7 and 8 in Part 2 (MAD) will be conducted to support a regulatory submission after subjects complete Day 39 for safety data or Day 17 for PK data.

Disposition, demographic and baseline characteristics, and safety outputs to be generated for the interim analysis will have the same format as the final outputs for the CSR, with the exception of being presented by cohort instead of treatment with no placebo due to the blinded nature of the analysis. The blind will be maintained for the disposition, demographic and baseline characteristics, and safety outputs by presenting all outputs by cohort instead of treatment and no listings by treatment will be provided. Outputs to be provided for the interim analysis are indicated within the list of tables, listings, and figures in Appendix A.

The PK tables and figures will be provided in a blinded fashion without indicating subject number and will use nominal times. The analysis of the MAD PK data is to be performed by a third party vendor.

5 ANALYSIS POPULATIONS

5.1 Safety Population

The safety population will include all subjects who receive at least 1 dose study drug (ARN-75039 or placebo).

Subjects in the safety population will be analyzed as treated and the population will be used for demographic and baseline characteristics and safety summaries.

5.2 Pharmacokinetic Population

The PK population will include all subjects who receive any amount of ARN-75039 and have sufficient postdose concentration-time data.

Subjects in the PK population will be analyzed as treated and the population will be used for all PK summaries and analyses.

Data from subjects who significantly violate a protocol inclusion or exclusion criteria, deviate significantly from the protocol, or have unavailable or incomplete data, which may influence the PK analysis may be excluded from the PK population. Additionally, data from subjects who experience vomiting starting within 2 times the median T_{max} for the given dose level may be excluded from the summary statistics and analysis (for the affected treatment for the Food Effect Cohort). For Part 2, vomiting on non-intensive PK sampling Days (eg, Days 2-9) will be reviewed to determine if exclusion is necessary. Any subject or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

6 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

6.1 Subject Disposition and Discontinuation

The number of subjects who are randomly assigned to a treatment in the study and the number and percentage of subjects who complete the study will be presented for each study part, by treatment (food effect cohort presented as 1 treatment) and overall. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized for each study part, by treatment and overall for all randomly assigned subjects. The number of subjects included in each analysis population will be presented for each study part, by treatment, and overall.

A data listing for subject disposition, including study completion status and reason for study discontinuation, will be provided. In addition, analysis populations and reasons for exclusion from the analysis populations will be provided in a data listing.

6.2 Protocol Deviations

Protocol deviations will be captured in a log by the project manager, exported into a clinical dataset, and presented in a data listing. Deviations will be assigned as major or minor according to the following definitions:

- A major deviation from the protocol is defined as a deviation that potentially may significantly affect a subject's rights, safety or well-being, or had a potentially significant impact on the primary or key secondary efficacy endpoint(s) for that subject.
- A minor deviation from the protocol is defined as a deviation that does not potentially significantly affect a subject's rights, safety or well-being, or does not have a potentially significant impact on the primary or key secondary efficacy endpoint(s) for that subject.

The count and percentage for the number of subjects with at least 1 protocol deviation and the total number of deviations will be presented for each study part, by treatment and overall, for the safety population. A summary of the protocol deviations by protocol deviation coded term and study event will also be provided.

Protocol deviations will be assigned to a treatment based on the start date and/or time of the protocol deviation when compared with study drug administration dates and times or based on the visit if data and/or time is not available. Any protocol deviation not assigned to a treatment (ie, occurs before the first study drug administration) will be included in the data listing only.

6.3 Demographic and Baseline Characteristics

Descriptive statistics (Section 4.1) will be calculated for continuous demographic and baseline characteristic variables (age, height, weight, and body mass index [BMI] at Screening) and categorical demographic variables (sex, race, and ethnicity) for each study part, by treatment (food effect cohort presented as 1 treatment) and overall for the safety population.

An additional summary table will be included if the PK population differs from the safety population. If the populations are the same, 1 table will be presented and the title will be revised accordingly (ie, Demographic and Baseline Characteristics [Safety and PK Populations]).

A data listing will be presented for all demographic data. In addition, the baseline characteristics of weight, height, and BMI will be included in the vital signs data listing.

6.4 Medical History

Medical history data will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.1) to system organ class (SOC) and preferred term (PT) and will be listed by subject identifier, medical condition reported term, onset date, and ongoing status/resolution date. The MedDRA version utilized (25.1) will be provided in a footnote in the data listing.

6.5 Inclusion and Exclusion Criteria

Inclusion criteria not met and exclusion criteria met will be presented in a data listing.

7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

7.1 Plasma Concentrations

7.1.1 Pharmacokinetic Blood Sampling

Part 1 (SAD)

Blood samples for the determination of plasma concentrations of ARN-75039 will be collected from all subjects prior to and following administration of the single oral dose of ARN-75039 or placebo at the following time points: Day 1 predose and at 0.25 (15 minutes), 0.5 (30 minutes), 1, 2, 4, 6, 12, 24 (Day 2), 48 (Day 3), 72 (Day 4), 168 (Day 8), and 336 (Day 15/EOS) hours postdose.

Part 2 (MAD)

Blood samples for the determination of plasma concentrations of ARN-75039 will be collected from all subjects prior to and following repeat doses of ARN-75039 or placebo at the following time points:

- Day 1 & Day 10: predose and at 0.5 (30 minutes), 1, 2, 4, 6, 8, 10 (before the second daily dose), 12, 14, and 24 hours after the morning dose, with the 24-hour sample being collected prior to the morning dose on Day 2.
- Day 2 & 8: 6 hour post morning dose
- Day 3 & 8: predose morning dose
- Day 17 & 39: postdose sample (approximately 168 hours and 696 hours after the morning dose on Day 10)

Food Effect Cohort(s)

Blood samples for the determination of plasma concentrations of ARN-75039 will be collected from all subjects prior to and following administration of each dose of ARN-75039 or placebo at the following time points: Day 1 and Day 15 predose and at 0.25 (15 minutes), 0.5 (30 minutes), 1, 2, 4, 6, 12, 24 (Day 2/Day 16), 48 (Day 3/Day 17), 72 (Day 4/Day 18), 168 (Day 8/22), and 312 (Day 14/Day 29/EOS) hours postdose.

7.1.2 Bioanalytical Analysis

Plasma concentrations of ARN-75039 will be determined using a validated liquid chromatography-tandem mass spectrometry method at KCAS Bioanalytical Services (Olathe, KS). The expected analytical range for ARN-75039 in plasma is 25.0 to 10,000 ng/mL.

7.1.3 Concentration Data Presentation

Descriptive statistics (Section 4.1) for plasma ARN-75039 concentrations will be tabulated at each scheduled time point by treatment for the PK population. Mean plasma concentration-time

profiles will be plotted on linear (with and without SD bars) and semilogarithmic scales by study part. Mean (SD) trough concentrations vs time will also be plotted for Part 2. Mean figures for the Food Effect Cohort, with the fasted and fed treatments overlaid, will also be provided. Individual concentration-time plots will be presented. Spaghetti plots of the individual concentrations versus time will also be provided. For the Food Effect Cohort, individual plots will display the fed and fasted treatments overlaid, while the spaghetti plots will display the fed and fasted treatment separately. For Part 2 (MAD phase), the mean plots and spaghetti plots will display the 24-hour profiles on Days 1 and 10 on side-by-side panels, and spaghetti plots of morning troughs on Days 2 through 11 will be plotted. The individual plots will overlay the 24-hour profiles for Days 1 and 10.

Plasma concentrations that are BLQ will be treated as outlined in Section 4.2 for the computation of mean plasma concentration values and derivation of individual subject computed parameters.

All plasma concentrations will be presented in a data listing.

7.2 Plasma Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated from plasma concentration-time data using noncompartmental analysis in Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ), using actual sample times (Section 4.2).

The PK parameters to be calculated (data permitting) following single doses of ARN-75039 in Part 1 (including both study periods for the Food Effect Cohort) and following the first dose in Part 2 are described in Table 5. The PK parameters to be calculated (data permitting) following the first dose of ARN-75039 on Day 1 and10 for Part 2 are described in Table 6.

Table 5 Single-Dose Noncompartmental Pharmacokinetic Parameters to be Calculated for Part 1 (SAD), and Food Effect Cohort

Parameter	Definition and Calculation Method
$AUC_{0\text{-}12h}$	Area under the plasma concentration-time curve (AUC) from time 0 to 12 hours, calculated using linear trapezoidal method
$AUC_{0\text{-}24h}$	AUC from time 0 to 24 hours, calculated using linear trapezoidal method (Part 1, including Food Effect Cohort, and QD dosing for Part 2 only)
$AUC_{0\text{-}t}$	AUC from time 0 to time of the last quantifiable plasma concentration, calculated using linear trapezoidal method
$AUC_{0\text{-}\infty}$[a]	AUC from time 0 extrapolated to infinity, calculated as: $AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_{last}/\lambda_z$ Where C_{last} is the last quantifiable plasma concentration
AUC_{ext}[a]	Percentage of $AUC_{0\text{-}\infty}$ that is extrapolated from the time of the last quantifiable concentration to infinity, calculated as: $AUC_{ext} = ([AUC_{0\text{-}\infty} - AUC_{0\text{-}t}]/AUC_{0\text{-}\infty}) \times 100$ (a diagnostic parameter calculated and listed in the data listing, but not included in the descriptive statistics)

Parameter	Definition and Calculation Method
C_{max}	Maximum observed plasma concentration, obtained by inspection of individual subject concentration-time data
T_{max}	Time to reach C_{max}, obtained directly from the observed concentration-time data. If C_{max} occurs at more than 1 time point, T_{max} is defined as the first time point with this value.
T_{last}	Time of the last quantifiable plasma concentration, obtained directly from the observed concentration-time data
λ_z[a]	Terminal elimination rate constant, estimated by linear regression of logarithmically-transformed concentration-time data (The upper and lower limits and number of points used for the calculation of λ_z and the adjusted coefficient of determination [R^2_{adj}] for the linear regression will be included in the data listing for informational purposes, but not included in the descriptive statistics.)
$t_{1/2}$[a]	Terminal elimination half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$ Where ln is the natural logarithm
CL/F[a]	Apparent clearance after extravascular administration, calculated as: $CL/F = Dose/AUC_{0-\infty}$.
V_z/F[a]	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as: $V_z/F = Dose/(AUC_{0-\infty} \times \lambda_z)$
$DNAUC_{0-t}$	Dose-normalized AUC_{0-t}, calculated as: $DNAUC_{0-t} = AUC_{0-t}/Dose$ (Part 1, including Food Effect Cohort, only)
$DNAUC_{0-\infty}$[a]	Dose normalized $AUC_{0-\infty}$, calculated as: $DNAUC_{0-\infty} = AUC_{0-\infty}/Dose$ (Part 1, including Food Effect Cohort, only)
DNC_{max}	Dose-normalized C_{max}, calculated as: $DNC_{max} = C_{max}/Dose$ (Part 1, including Food Effect Cohort, only)

[a] Will only be calculated if the terminal elimination phase is apparent.

Table 6 Multiple-Dose Noncompartmental Pharmacokinetic Parameters to be Calculated for Part 2 (MAD)

Parameter	Definition and Calculation Method
AUC_{0-10h}	Area under the plasma concentration-time curve (AUC) from time 0 to 10 hours following the morning dose, calculated using linear trapezoidal method, calculated for Day 1 and Day 10.

Parameter	Definition and Calculation Method
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve (AUC) from time 0 to 24 hours following the morning dose, calculated using linear trapezoidal method, calculated for Day 1 and Day 10.
$C_{max0\text{-}10h}$	Maximum observed plasma concentration during the 0-10 hour interval following the morning dose, obtained by inspection of individual subject concentration-time data, calculated for Day 1 and Day 10.
$T_{max0\text{-}10h}$	Time to reach $C_{max0\text{-}10h}$, obtained directly from the observed concentration-time data. If $C_{max0\text{-}10h}$ occurs at more than 1 time point, $T_{max0\text{-}10h}$ is defined as the first time point with this value.
$C_{max0\text{-}24h}$	Maximum observed plasma concentration during the 0-24 hour interval following the morning dose, obtained by inspection of individual subject concentration-time data, calculated for Day 1 and Day 10.
$T_{max0\text{-}24h}$	Time to reach $C_{max0\text{-}24h}$, obtained directly from the observed concentration-time data. If $C_{max0\text{-}24h}$ occurs at more than 1 time point, $T_{max0\text{-}24h}$ is defined as the first time point with this value.
$C_{min4\text{-}12h}$	Lowest observed plasma concentration from 4 to 12 hours following the morning dose on Day 1, obtained by inspection of individual subject concentration-time data.
$T_{min4\text{-}12h}$	Time to reach $C_{min4\text{-}12h}$, obtained directly from the observed concentration-time data. If $C_{min4\text{-}12h}$ occurs at more than 1 time point, $T_{min4\text{-}12h}$ is defined as the first time point with this value.
$C_{6h\ (Day\ 2)}$	Concentration at 6 hours following the morning dose on Day 2.
$C_{6h\ (Day\ 8)}$	Concentration at 6 hours following the morning dose on Day 8.
$C_{trough\ (Day\ 2)}$ $C_{trough\ (Day\ 3)}$ $C_{trough\ (Day\ 8)}$ $C_{trough\ (Day\ 10)}$ $C_{trough\ (Day\ 11)}$	Concentration prior to the morning dose on Days 2, 3, 8, and 10, and the 24-hour concentration on Day 11, obtained by inspection of individual subject concentration-time data; if the C_{trough} is missing, C_{trough} may be determined using interpolation/extrapolation (if applicable).
$DNAUC_{0\text{-}10h}$	Dose-normalized $AUC_{0\text{-}10h}$ (for Day 10 only), calculated as: $DNAUC_{0\text{-}10h} = AUC_{0\text{-}10h}/Dose$
$DNC_{max0\text{-}10h}$	Dose-normalized C_{max} (for Day 10 only), calculated as: $DNC_{max0\text{-}10h} = C_{max0\text{-}10h}/Dose$

PK parameters will not be calculated for subjects with fewer than 3 quantifiable postdose concentrations.

Additional noncompartmental PK parameters may be calculated and compartmental modeling may be performed, as necessary, to fully characterize the PK profile of ARN-75039, as deemed appropriate by the pharmacokineticist.

Individual subject T_{max} and T_{min} values will be presented with 2 decimal places; C_{6h},C_{max}, C_{min}, and C_{trough} will be presented to the precision of the raw bioanalytical data; and all other parameters will be presented with 3 significant figures. Descriptive statistics (Section 4.1) of PK parameters for ARN-75039 will be provided for the PK population by study part, day (as applicable), and treatment. All calculated PK parameters will be presented in a data listing.

7.3 Assessment of Dose Proportionality

A formal statistical analysis will be performed on the PK parameters for Part 1 ($AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}; fed portion only for the food effect cohort) and for the morning dose on Day 10 for Part 2 ($AUC_{0\text{-}10h}$ and $C_{max0\text{-}10h}$) in order to assess the dose proportionality of the treatments for the PK population. Additional parameters (eg, $AUC_{0\text{-}12h}$ and/or $AUC_{0\text{-}24h}$) may be analyzed, as necessary, to fully characterize the dose proportionality, as deemed appropriate by the pharmacokineticist. Data will be analyzed separately by Part and Day (as applicable). Dose proportionality will be assessed using the following analysis of variance (ANOVA) model with natural logarithm (ln) transformed values: ln(parameter) = μ + β × ln(dose). This model is often referred to as a power model, since after exponentiation the formula is: parameter = α × dose$^{\beta}$. An estimate of the slope (β), which measures the proportionality between the dose and the PK parameters, will be presented along with a 90% CI for β. Dose proportionality will be assessed by comparing the 90% CI for β to the critical region generated using the following formula:

$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta < 1 + \frac{\ln(\theta_H)}{\ln(r)}$, where $\theta_L = 0.80$, $\theta_H = 1.25$, and r is the ratio of the highest to the lowest dose levels included. If the 90% CI for β lies entirely within the critical region, then dose proportionality will be concluded over the dose range under analysis.

The SAS PROC MIXED code is as follows:

```
PROC MIXED data=adpp method=reml order=internal;
    BY paramn paramcd paraml avisit;
    MODEL ln_aval = ln_dose / solution outp=pred ddfm=kr cl alpha = 0.1 alphap=0.1;
    ODS output solutionf=est;
RUN;
```

Slope estimates and 90% CIs for β will be presented to 3 decimal places.

Figures will also be presented for each parameter included in the models above, showing the observed values, predicted fit, and 90% CIs.

If only 2 dose-levels are available, then an alternative evaluation of dose proportionality will be conducted using an ANOVA model on the dose normalized, ln-transformed PK parameter values. The model will include dose as a fixed effect. The two-sided 90% CI for the ratio of dose comparisons will be constructed.

The SAS PROC MIXED code is as follows:

```
PROC MIXED data=adpp method=reml order=internal;
    BY paramn paramcd paraml avisit ;
    CLASS trta ;
    MODEL ln_aval = trta / ddfm=kr ;
```

```
    ESTIMATE ‘Dose 1 vs. Dose 2’ trta 1 -1 /cl alpha=0.10 ;
    LSMEANS trta;
RUN;
```

The geometric least-squares mean ratios (GLSMRs) will be presented to 1 more level of precision than the reported values and the 90% CIs will be reported to 2 decimal places.

Box plots of dose-normalized PK parameters will be presented by study part. Parameters will include $DNAUC_{0\text{-}t}$, $DNAUC_{0\text{-}\infty}$, and DNC_{max} for Part 1 and $DNAUC_{0\text{-}10h}$ and $DNC_{max0\text{-}10h}$ for Part 2. Additional parameters may be included, based on which parameters are included in the models above, as applicable.

7.4 Assessment of Food Effect (Food Effect Cohort)

To evaluate the effect of food on the PK of ARN-75039, a mixed-effects model will be utilized using the ln-transformed values of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} parameters for the PK population, for data from the Food Effect Cohort. The model will include treatment (fed or fasted) as a fixed effect and subject as a random effect. Treatment least-squares (LS) mean differences and 90% CIs for the difference between fed and fasted will be constructed for the ln-scale values of each parameter, back transformed, and expressed as the GLSMR. The GLSMR and 90% CIs for each PK parameter will be presented.

The SAS PROC MIXED code is as follows:

```
PROC MIXED data=adpp;
    BY paramn paramcd param;
    CLASS usubjid trta;
    MODEL ln_aval=trta /ddfm=kr;
    RANDOM usubjid;
    ESTIMATE 'Fed vs. Fasted'  trta  1  –1 / cl alpha=0.10;
RUN;
```

The GLSMRs will be presented to 1 more level of decimal precision than the reported values, 90% CIs will be reported to 2 decimal places, and p-values will be presented with 4 decimal places.

Additional PK parameters (eg, $AUC_{0\text{-}12h}$ and/or $AUC_{0\text{-}24h}$) may be analyzed, as necessary to assess the effect of food on the PK of ARN-75039.

Box plots of PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and T_{max}) will be presented by treatment for the Food Effect Cohort. Additional parameters may be included, based on which parameters are included in the mixed-effects model above, as applicable.

8 SAFETY AND TOLERABILITY ANALYSES

8.1 Adverse Events

Version 25.1 of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events. Verbatim adverse event descriptions will be mapped to MedDRA Lowest Level Terms (LLT) based on medical judgement. Each LLT is associated (in MedDRA) with a unique Preferred Term (PT), and that PT to a primary System Organ Class (SOC).

A TEAE is defined as any event that starts on or after the first dose of study drug. All AEs captured in the database will be presented in by-subject data listings; however, only TEAEs will be summarized. An additional data listing will be provided for AEs leading to study discontinuation.

Adverse events will be assigned an associated treatment based on the onset date and time. Any AEs that occur after the first study drug administration will be considered treatment-emergent. For the food effect cohort, any AEs that occur after the first study drug administration but before the second study drug administration will be considered treatment-emergent to the dosing level under fed conditions. Any AEs that occur after the second study drug administration will be considered treatment-emergent to the dosing level under fasted conditions. In addition, adverse events of special interest (AESI) will be collected for Part 2.

An overall summary of TEAEs will be provided summarizing subjects with at least 1 of the following: TEAE, study drug-related TEAE, grade 2 moderate or higher TEAE, AESIs (Part 2 only), TESAE, study drug-related grade 2 moderate or higher TEAE, study drug-related AESIs (Part 2 only), study drug-related TESAE, TEAE leading to study discontinuation, and study drug-related TEAE leading to study discontinuation as well as the number of events within each of the previously mentioned categories, for each study part by treatment and overall.

In addition, summaries of unique TEAEs will be presented by SOC, PT, treatment, and overall for each study part and will include the number and percentage of subjects who experienced the unique event for all TEAE PTs, all TEAE PTs by relationship, all TEAE PTs by maximum severity grade, study drug-related TEAE PTs by maximum severity grade, and all TEAEs leading to study discontinuation. For Part 2, additional summary tables will be provided by treatment and overall for all AESIs by SOC and PT, AESIs by maximum severity grade, and AESIs leading to study discontinuation. Additionally, if more than 1 serious TEAE occurs during a study part, a summary of all serious TEAEs will be provided by SOC, PT, and relationship for each study part by treatment and overall.

Study drug-related TEAEs include all those classified by the investigator as having reasonable possibility of being related to study drug. For the purposes of summarization, AEs assessed as being ‘Definitely related’, ‘Probably related’, or ‘Possibly related’ will be considered related. Adverse events assessed as being ‘Unlikely related’ or ‘Not related’ will be considered unrelated. Events for which the investigator did not record the relationship to study drug will be considered related to study drug. For summaries by relationship, the most related event will be selected.

The severity of each AE will be assessed by the investigator and graded according to the

Common Terminology Criteria for Adverse Events (CTCAE) (v5.0; Department of Health and Human Services, National Institutes of Health, National Cancer Institute [NCI] [United States] 2017). Severity for event terms not listed in the NCI CTCAE will be evaluated by the investigator as mild, moderate, severe, life threatening, or death. For summaries by severity, the most severe event classification will be selected.

Multiple events mapping to the same PT will be counted only once per subject in each of the previously mentioned summaries for each part by treatment and overall. In the presentation, SOC and PT (within each SOC) will be sorted in order of descending frequency (by overall percentage of unique TEAEs) and then in alphabetical order, if necessary, to break ties.

The MedDRA version (25.1) will be provided in a footnote in both tables and data listings.

8.2 Vital Sign Measurements

Systolic and diastolic blood pressure, pulse, respiratory rate, and oral body temperature and in Part 2 only weight, BMI and waist measurement will be measured at baseline and each scheduled postbaseline time point. Results and change from baseline will be summarized for each study part by treatment and time point using descriptive statistics (Section 4.1), where baseline is defined as stated in Section 4.3.

If a parameter is repeated for a time point, the last value reported for the time point will be used in the summary. Unscheduled assessments that are not used for baseline will not be included in summary tables; however, all vital sign measurements will be presented in a data listing by date.

8.3 Clinical Laboratory Assessments (Hematology, Serum Chemistry, Coagulation, and Urinalysis)

Clinical laboratory evaluations of hematology, serum chemistry, coagulation, and urinalysis will be performed. Results and change from baseline will be summarized for each study part by treatment and time point using descriptive statistics (Section 4.1) for numeric parameters and counts and percentages for categorical parameters, where baseline is defined as stated in Section 4.3. Values reported as "<X" or ">X", where X is a numerical value will be converted to the numerical value of "X" and summarized (eg, a value reported as "<5" would be summarized as a value of 5).

In addition, posttreatment clinical laboratory categorical changes (shifts) from the baseline categorical range (baseline value as defined in Section 4.3) will be presented by parameter, using the count and percentage of subjects with clinical laboratory test results below, within, and above normal ranges and tabulated for each study part by treatment.

In addition, clinically significant laboratory values (as determined by the investigator) will be presented in a data listing and will include all values for a given parameter for subjects who have at least 1 postbaseline clinically significant value.

Unscheduled assessments that are not used for baseline will not be included in summary tables; however, all clinical laboratory data will be presented in data listings in chronological order, by date for unscheduled or repeated values.

8.4 Safety 12-Lead Electrocardiograms

Safety 12-lead ECG including ECG heart rate, PR, QRS, QT, QT interval corrected for heart rate using Bazett's formula, QT interval corrected for heart rate using Fridericia's formula (QTcF), and RR will be collected at baseline and each scheduled postbaseline time point. Results and change from baseline will be summarized for each study part by treatment and time point using descriptive statistics Section 4.1, where baseline is defined as stated in Section 4.3. Individual results will be interpreted as normal, abnormal not clinically significant, or abnormal clinically significant and the worst interpretation at each time point will be summarized for each study part by treatment and time point using counts and percentages.

When triplicate ECGs are measured, results will be averaged and rounded to 1 decimal place before summarization. When interpretations are summarized for triplicate ECGs, the worst interpretation of the 3 will be used for summarization.

A categorical summary of QTcF will be provided using counts and percentages at baseline, maximum postbaseline value, and maximum change from baseline value, including unscheduled assessments, for each study part by treatment for the following categories:

- Result ≤450 ms
- Result >450 and ≤480 ms
- Result >480 and ≤500 ms
- Result >500 ms
- Change from baseline ≤30 ms
- Change from baseline >30 and ≤60 ms
- Change from baseline >60 ms

Unscheduled assessments that are not used for baseline will not be included in summary tables, except as described previously; however, all safety 12-lead ECG values and interpretations will be presented in a data listing, by date and time for unscheduled values.

8.5 Colonic Transit Test (Sitzmarks x-ray)

The assessment of colonic motility using SITZMARKS® involves administering a capsule to subjects and evaluating the expulsion of radiopaque markers over a 5-day period in Part 2 (MAD) of the study.

Colonic transit test will be collected at screening and on Day 7. Results and change from screening will be summarized for Part 2 by treatment using descriptive statistics Section 4.1.

Unscheduled assessments that are not used for baseline will not be included in summary tables; however, all results will be presented in a data listing.

8.6 Physical Examination Findings

The physical examination findings will be presented in a data listing by subject, and abnormal findings will be flagged for clinical significance based on the investigator's judgment. Posttreatment findings will be presented as normal, abnormal, or not done summarized with counts and percentages for each study part by treatment and time point for each body system.

8.7 Prior and Concomitant Medications

Prior and concomitant medications will be classified according to the World Health Organization (WHO) Drug dictionary (September 2022 Version) and presented in a data listing by Anatomical Therapeutic Chemical Class Level 3 and preferred drug name. The WHO Drug dictionary version will be provided in a footnote in the data listing.

Medications with a start and end date/time occurring before the first drug administration date/time will be classified as prior medications. Medications with an end date/time occurring on or after the first drug administration date/time, or that have unknown or ongoing end date/times, will be classified as concomitant medications. In the event of a partial date/time, it will be compared with the first drug administration date/time and if the year and/or month is clearly before the first drug administration date, and the medication's end date is partial, but clearly before the first drug administration date/time then the medication will be classified as a prior medication. However, if the partial date overlaps with the first drug administration date as having the same year and/or month then the medication will be classified as a concomitant medication.

8.8 Extent of Exposure

The extent of exposure will be summarized in terms of the number and percentage of subjects treated in each study part by treatment and overall. For Part 2, the number of doses and the cumulative dose received will be summarized with descriptive statistics (Section 4.1) by treatment and overall.

Study drug administration dates and times will be presented in a data listing.

8.9 Ophthalmologic Examinations

Ophthalmologic examinations will be performed. The examination will include Snellen Acuity testing, pupillary reflexes, slit-lamp examination, intraocular pressure, and dilated fundus examination.

The ophthalmologic examination findings will be presented in a data listing by subject, and abnormal findings will be flagged for clinical significance based on the investigator's judgment.

8.10 Meal Administration

Meal administration start/stop times and amount of meal consumed, will be provided in data listings by subject.

8.11 Ancillary Data Listings

Serology (HIV and hepatitis) screen results, urine drug and alcohol screen results, serum pregnancy test and follicle-stimulating hormone test results, and coronavirus disease 2019 (COVID-19) screen results will be presented in data listings.

8.12 Clinical Questionnaire

The clinical questionnaire assessment will be collected at screening and each scheduled postbaseline visit. Results will be summarized for Part 2 only by treatment and visit using descriptive statistics (Section 4.1) for continuous variables and counts and percentages for categorical variables. The clinical questionnaire will be provided in a data listing by subject.

9 CHANGES FROM PROTOCOL PLANNED ANALYSIS

Section 11.8 of the protocol outlines that change values for vital signs will be calculated based on the Day -1 vital sign results. Baseline for vital signs measurements are the vital signs that are taken within 60 minutes of dosing and change will be calculated based on the predose vital signs instead of the Day -1 vital signs.

10 REFERENCES

Campbell MJ, Gardner MJ. Calculating confidence intervals for some non-parametric analyses. Br Med J (Clin Res Ed). 1988. 296(6634):1454-6. doi: 10.1136/bmj.296.6634.1454 .

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, dated 27 November 2017. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Accessed 10 March 2023. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX A: LIST OF TABLES, LISTINGS, AND FIGURES

Shells of the tables, listings, and figures will be provided as a separate document. Titles may change slightly from what is presented here in this appendix.

While this appendix is designed to give the reader an understanding of what is intended to be presented, in creating the tables, listings, and figures, modification in presentation may be necessary to adhere to the actual data collected. Any updates will be detailed in the shell document.

Items to be provided for the safety outputs for the interim analysis for Part 1 can be identified within this list by the * after the output number and items to be provded for the safety outputs for the interim analysis for Part 2 can be identified within this list by the # after the output number.

14 TABLES, LISTINGS, AND FIGURES REFERRED TO BUT NOT PRESENTED IN THE TEXT

14.1 Disposition and Demographic Data Summary Tables

Table 14.1.1.1* Subject Disposition – Part 1 (Safety Population)
Table 14.1.1.2# Subject Disposition – Part 2 (Safety Population)
Table 14.1.2.1* Demographic and Baseline Characteristics – Part 1 (Safety Population)
Table 14.1.2.2^ Demographic and Baseline Characteristics – Part 1 (PK Population)
Table 14.1.2.3# Demographic and Baseline Characteristics – Part 2 (Safety Population)
Table 14.1.2.4^ Demographic and Baseline Characteristics – Part 2 (PK Population)
^*Include only if the PK populations for the respective parts differ from the safety populations. If the populations are the same, adjust the table numbering to ensure consecutive ordering and update the population portion of the table title to (Safety and PK Populations).*
Table 14.1.3.1 Summary of Protocol Deviations – Part 1 (Safety Population)
Table 14.1.3.2 Summary of Protocol Deviations – Part 2 (Safety Population)

14.2 Plasma Concentration and Pharmacokinetic Summaries, Analyses, and Figures

Table 14.2.1.1 Summary of Plasma Concentrations – Part 1 (PK Population)
Table 14.2.1.2 Summary of Plasma Concentrations – Part 2 (PK Population)
Table 14.2.2.1 Summary of Plasma Pharmacokinetic Parameters – Part 1 (PK Population)
Table 14.2.2.2 Summary of Plasma Pharmacokinetic Parameters – Part 2 (PK Population)
Table 14.2.3.1 Summary of Dose-Proportionality Analysis – Part 1 (PK Population)
Table 14.2.3.2 Summary of Dose-Proportionality Analysis – Part 2 (PK Population)
Table 14.2.4 Summary of Food-Effect Analysis – Part 1 (PK Population)
Figure 14.2.1.1 Mean Plasma ARN-75039 Concentration-Time Profile, Linear Scale – Part 1 (PK Population)
Figure 14.2.1.2 Mean Plasma ARN-75039 Concentration-Time Profile Following 300 mg ARN-75039 Administered Under Fasted and Fed Conditions, Linear Scale – Part 1 (PK Population)
Figure 14.2.1.3 Mean Plasma ARN-75039 Concentration-Time Profile, Linear Scale – Part 2 (PK Population)
Figure 14.2.1.4 Mean ±SD Plasma ARN-75039 Morning Trough Concentrations Versus Time, Linear Scale – Part 2 (PK Population)
Figure 14.2.2.1 Mean Plasma ARN-75039 Concentration-Time Profile, Semilogarithmic Scale – Part 1 (PK Population)
Figure 14.2.2.2 Mean Plasma ARN-75039 Concentration-Time Profile Following 300 mg ARN-75039 Administered Under Fasted and Fed Conditions, Semilogarithmic Scale – Part 1 (PK Population)
Figure 14.2.2.3 Mean Plasma ARN-75039 Concentration-Time Profile, Semilogarithmic Scale – Part 2 (PK Population)
Figure 14.2.3.1 Dose-Proportionality Plots of Plasma ARN-75039 Pharmacokinetic Parameters – Part 1 (PK Population)

14.3 Safety Data Summary Tables

14.3.1 Adverse Events

Table 14.3.1.6.3# Treatment-Emergent Adverse Events of Special Interest Leading to Study Discontinuation by System Organ Class, Preferred Term, and Relationship to Study Drug – Part 2 (Safety Population)

Table 14.3.1.7.1^ Serious TEAEs by System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1 (Safety Population)
^Include only if more than 1 serious TEAE is reported. Follow the same format as Table 14.3.1.3.1.

Table 14.3.1.7.2^ Serious TEAEs by System Organ Class, Preferred Term, and Relationship to Study Drug – Part 2 (Safety Population)
^Include only if more than 1 serious TEAE is reported. Follow the same format as Table 14.3.1.3.1.

14.3.2 Listing of Deaths, Other Serious, and Significant Adverse Events

Listing 14.3.2.1*# Serious Adverse Events and Deaths (Safety Population)

14.3.3 Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events

Provided by the clinic, if applicable.

14.3.4 Abnormal Laboratory Value Listing

Listing 14.3.4.1*# Clinically Significant Laboratory Results (Safety Population)

14.3.5 Other Observations Related to Safety

Table 14.3.5.1.1 Vital Sign Results and Change From Baseline – Part 1 (Safety Population)
Table 14.3.5.1.2 Vital Sign Results and Change From Baseline – Part 2 (Safety Population)
Table 14.3.5.2.1 Hematology Parameter Results and Change From Baseline – Part 1 (Safety Population)
Table 14.3.5.2.2 Hematology Parameter Results and Change From Baseline – Part 2 (Safety Population)
Table 14.3.5.3.1* Hematology Parameter Shifts From Baseline – Part 1 (Safety Population)
Table 14.3.5.3.2# Hematology Parameter Shifts From Baseline – Part 2 (Safety Population)
Table 14.3.5.4.1 Serum Chemistry Parameter Results and Change From Baseline – Part 1 (Safety Population)
Table 14.3.5.4.2 Serum Chemistry Parameter Results and Change From Baseline – Part 2 (Safety Population)
Table 14.3.5.5.1* Serum Chemistry Parameter Shifts From Baseline – Part 1 (Safety Population)
Table 14.3.5.5.2# Serum Chemistry Parameter Shifts From Baseline – Part 2 (Safety Population)
Table 14.3.5.6.1 Coagulation Parameter Results and Change From Baseline – Part 1 (Safety Population)
Table 14.3.5.6.2 Coagulation Parameter Results and Change From Baseline – Part 2 (Safety Population)
Table 14.3.5.7.1* Coagulation Parameter Shifts From Baseline – Part 1 (Safety Population)

16.1 Study Information

Appendix 16.1.7.1 Randomization Schedule
Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1.1 Subject Disposition

16.2.2 Protocol Deviations

Appendix 16.2.2.1 Protocol Deviations

16.2.3 Subject Populations and Excluded Reasons

Appendix 16.2.3.1 Subjects in the Safety and PK Populations and Exclusion Reasons

16.2.4 Demographic Data

Appendix 16.2.4.1 Demographic and Baseline Characteristics
Appendix 16.2.4.2 Inclusion Criteria Not Met/Exclusion Criteria Met
Appendix 16.2.4.3 Medical History
Appendix 16.2.4.4 Prior and Concomitant Medications

16.2.5 Compliance and Drug Concentration Data

Appendix 16.2.5.1 Study Drug Administration
Appendix 16.2.5.2 Plasma Pharmacokinetic Concentrations and Sampling Times

16.2.6 Pharmacokinetic Data

Appendix 16.2.6.1 Plasma Pharmacokinetic Parameters
Appendix 16.2.6.2.1 Spaghetti Plots of Individual Plasma ARN-75039 Concentration-Time Profiles, Linear Scale – Part 1
Appendix 16.2.6.2.2 Spaghetti Plots of Individual Plasma ARN-75039 Concentration-Time Profiles, Linear Scale – Part 2
Appendix 16.2.6.3.1 Spaghetti Plots of Individual Plasma ARN-75039 Concentration-Time Profiles, Semilogarithmic Scale – Part 1
Appendix 16.2.6.3.2 Spaghetti Plots of Individual Plasma ARN-75039 Concentration-Time Profiles, Semilogarithmic Scale – Part 2
Appendix 16.2.6.3.3 Spaghetti Plots of Individual Plasma ARN-75039 Morning Trough Concentrations Versus Time, Linear Scale – Part 2
Appendix 16.2.6.4.1 Individual Plasma ARN-75039 Concentration-Time Profiles, Linear Scale – Part 1
Appendix 16.2.6.4.2 Individual Plasma ARN-75039 Concentration-Time Profiles, Linear Scale – Part 2
Appendix 16.2.6.5.1 Individual Plasma ARN-75039 Concentration-Time Profiles, Semilogarithmic Scale – Part 1

Appendix 16.2.6.5.2 Individual Plasma ARN-75039 Concentration-Time Profiles, Semilogarithmic Scale – Part 2

16.2.7 Adverse Events and Other Safety Data

Appendix 16.2.7.1 Adverse Events
Appendix 16.2.7.2 Adverse Events Leading to Study Discontinuation
Appendix 16.2.7.3 Vital Sign Measurements
Appendix 16.2.7.4 Safety 12-Lead ECG Results
Appendix 16.2.7.5 Physical Examination Findings
Appendix 16.2.7.6 Ophthalmologic Examination Findings
Appendix 16.2.7.7 Meal Administration
Appendix 16.2.7.8 Colonic Transit Test Results
Appendix 16.2.7.9 Clinical Questionnaire Results

16.2.8 Individual Laboratory Safety Response Data

Appendix 16.2.8.1 Clinical Laboratory Results for Hematology
Appendix 16.2.8.2 Clinical Laboratory Results for Serum Chemistry
Appendix 16.2.8.3 Clinical Laboratory Results for Coagulation
Appendix 16.2.8.4 Clinical Laboratory Results for Urinalysis
Appendix 16.2.8.5 Urine Drug and Alcohol Screen Results
Appendix 16.2.8.6 Serology (HIV and Hepatitis) Screen Results
Appendix 16.2.8.7 Serum Pregnancy and Follicle-Stimulating Hormone Test Results (Female Subjects Only)
Appendix 16.2.8.8 COVID-19 Test Results

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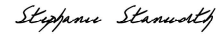
Stephanie Stanworth stephanie.stanworth@spauldingclinical.com Associate Director, Biostatistics Spaulding Clinical Research, LLC Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 89D262FE-3ACF-44A1-9F24-0DB1F38DC01D Using IP Address: 24.11.4.143 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 6/14/2024 12:01:39 PM Viewed: 6/14/2024 12:01:57 PM Signed: 6/14/2024 12:02:15 PM
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Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	6/14/2024 12:02:15 PM
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