Statistical Analysis Plan

Protocol No. ARN-75039-103, 29 January 2025

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

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Glossary and Abbreviations

Abbreviation	Term
AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration vs time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	~~area~~ Area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours post-dosing
BMI	Body mass index
BQL	Below the lower limit of quantification
CI(s)	Confidence interval(s)
CL/F	Apparent clearance
C_{max}	Maximum observed plasma concentration
$C_{min0-24}$	Minimum observed plasma concentration from time zero to 24 hours post-dose
cm	Centimeter
CTCAE	Common Terminology Criteria for Adverse Events
CRU	Clinical Research Unit
CV %	Coefficient of variation (%)
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ET	Early Termination
FDA	Federal Drug Administration
h or hr	Hour(s)
HEENT	Head, ears, eyes, nose, and throat
HPMC	Hydroxypropyl methylcellulose
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IP	Investigational Product
kg	Kilogram(s)
MRT	Mean Residence Time

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
m^2	Meter squared
n or N	Number of participants
NCA	Noncompartmental analysis
T	Oral Temperature
PE	Physical examination
PK(s)	Pharmacokinetic(s)
PR	Pulse Rate
RR	Respiratory Rate
SAS	Statistical Analysis Software
SD	Standard deviation
SAE(s)	Serious Adverse Event (s)
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOA	Schedule of assessments
TEAE(s)	Treatment emergent adverse event(s)
TESAE	Treatment-emergent serious adverse event
TLFs	Tables, Listings, and Figures
t_{max}	Time to maximum observed plasma concentration
$t_{½}$	Terminal elimination half-life
V_z/F	Apparent volume of distribution
WHO	World Health Organization
λ_z	Terminal-phase rate constant

1 Introduction

This is a comparative, randomized, single dose, 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.

This Statistical Analysis Plan (SAP) covers the detailed procedures for performing the Safety and PK statistical analyses and for producing the Tables, Listings, and Figures (TLFs) in the study. The templates in the TLF Shells are followed once the SAP is signed. The TLFs will be based on the templates/shells and only minor changes to TLFs will occur once the SAP is final (this includes footnotes due to data issues).

Relevant ICH and FDA guidance for statistical approaches will be followed.

The electronic case report form (eCRF) and external data files (PK concentrations from Frontage Labs and PK parameters from Frontage Clinical Services) will be included in the SDTM and ADaM datasets and these will be used to create the Tables, Listings and Figures (TLFs) as specified in the TLF Shells document.

2 Study Objectives

2.1 Primary Objective

- To compare the pharmacokinetic (PK) 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.

2.2 Secondary Objective

- To provide additional information on the safety and tolerability of ARN-75039 administered orally in healthy participants.

2.3 Endpoints

Primary:

- Relative bioavailability comparison of 300 mg neat ARN-75039 in HPMC capsules (Treatment A; reference) to 300 mg ARN-75039 with excipients tablets (Treatment B; comparator) 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:
    - Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{0-t}).
    - Area under the plasma concentration-time curve from time zero to 24 hours post-dose (AUC_{0-24}).
    - Area under plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).
    - Maximum observed plasma concentration (C_{max}).

- Minimum observed plasma concentration from time zero to 24 hours post-dose $C_{min0-24}$.
- Time to reach C_{max} (t_{max}).
- Half-life ($t_{1/2}$).
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the terminal phase after extravascular administration (V_z/F).

Secondary:

- 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 Study Design and Methods

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 assessments of vital signs, clinical laboratory values, and ECGs.

A total of 16 participants were randomized 1:1 into one of the following two sequences:

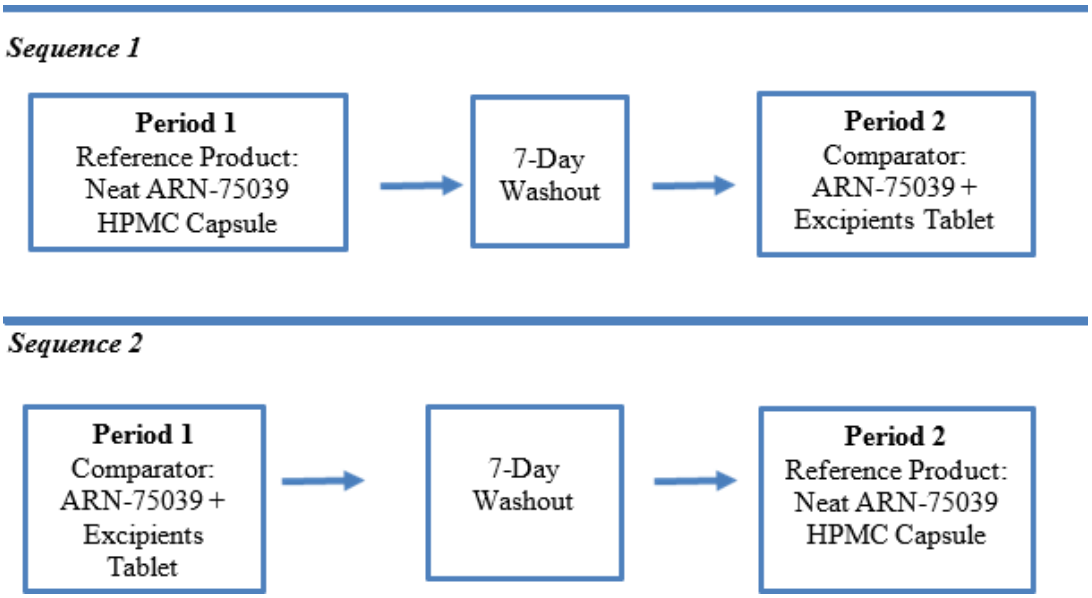
Sequence 1:

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

Sequence 2:

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

A study scheme is provided below:



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 sequence of 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 standardized meal. Participants will be dosed on Day 1 and Day 8 with a 7-day wash out period between the two dosing days. Pharmacokinetic (PK) assessments will be performed according to the Schedule of Assessments (SOA) (Table 1).

Table 1: Schedule of Assessments

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]	
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

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]	
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	
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 hours 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).

3.1 Study Assessments

3.1.1 Pharmacokinetic Assessments

The primary pharmacokinetic assessments are based on ARN-75039 plasma concentrations.

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 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).

The actual sampling time will be used for estimating PK parameters.

3.1.2 Safety Assessments

Safety assessments include the incidence of treatment emergent events (TEAE); study completion and discontinuation information; vital signs; height, weight, and body mass index (BMI), and physical examination (PE); clinical laboratory values, and ECG Medical observations, and adverse events reporting will be recorded by clinic staff throughout the study. Any safety assessment may be repeated at the discretion of the Investigator.

3.2 Randomization

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.

A randomization schedule was generated programmatically by the statistician prior to the start of the study, displaying subject assignments to each sequence with a unique Subject Identification Number. Eligible participants will be preassigned an Identification Number sequentially according to the time of arrival at admission to the clinical research unit (CRU). Once subject eligibility is confirmed, the Identification Number is assigned and may not be re-used. The date and time of the dosing will be recorded in the electronic case report form eCRF.

Participants who are unable to complete the sequence may be replaced and/or additional participants may be included at the discretion of the Sponsor. Replacement participants will be assigned to the same sequence as the participant who did not complete the study but will be assigned a new Identification Number.

3.3 Sample Size Justification

The sample size of 16 evaluable participants proposed for this study was not based on statistical analysis assessments but was 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 drug-related TEAE during the Treatment Period may be replaced as necessary to obtain 16 evaluable participants at the end of the clinical study.

3.4 Data Handling

Summaries for continuous variables will include the descriptive statistics for number of participants (n), mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (%), minimum (min), median, and maximum (max). Summaries for categorical (discrete) variables will include the number and/or percentage of participants in a specific category.

Conventions for presentation of numerical data in safety outputs (data collected in eCRF) are as follows:

- Minimum and maximum values will be presented to the same number of decimal places as (eCRF) data.
- Means and medians will be presented to one more decimal place than the eCRF data. Standard deviations will be presented to two more decimal places than the eCRF data.

For Plasma concentrations and PK parameters summary tables, if sample size n is >=2, then a value will be presented for a statistic in the summary tables but if n is less than 2 (n=1), then a dash will be used in place of the value.

Plasma concentrations and PK parameters in tables and listings will be displayed with 3 significant figures as follows:

- Values ≥ 0.0001 and < 1 will be reported with 3 significant figures (e.g., 0.0123).
- Values ≥ 1 and < 10 will be reported with 3 significant figures (e.g., 1.02).
- Values ≥ 10 and < 100 will be reported with 3 significant figures (e.g., 10.2).
- Values ≥ 100 and < 1000 will be reported with 3 significant figures (e.g., 102).
- Values ≥ 1000 will be reported with 3 significant figures (e.g., 1020).
- Values = 0 will be reported as 0 (applies only for listing)
- Values for t_{max} will be reported using one decimal place (2 significant figures).

For Safety Endpoints:

Baseline is defined as the last value measured prior to the first dose of study drug for each period. For safety parameters that are measured during each study period, the baseline is defined as the value prior to the first dose of each period.

Change from Baseline is defined as [Post-baseline Value – Baseline Value].

4 Data Analysis

4.1 Analysis Populations

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

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.

Any participant with pre-dose concentrations of ARN-75039 will be presented in the individual plasma concentration and PK listings but excluded from summary plasma concentrations, and PK summary table descriptive statistics if the pre-dose concentration is greater than 5% of the C_{max} value for that participant of that same period.

Participants who vomit within 4 hours post-dose will be excluded from PK statistical analysis for that period.

The frequency and percentage of participants in each population will be summarized. The listing will include all participants.

4.2 Study Participants

All safety summary tables will be presented as specified in the sections outlined below. All safety listings will include all subject data.

Disposition

Disposition will be summarized for the randomized participants by the following: using the number and percent of participants who complete the study; the number and percent of participants who discontinue the study; the reasons for discontinuation by treatment sequence; and Total. Eligibility status, disposition, and completion status will be listed for all randomized participants.

Protocol Deviations

Protocol deviations will be identified prior to database lock and may include but are not limited to: inclusion/exclusion violation; use of restricted medication; or not following clinical trial protocol procedures (includes: assessment not performed per protocol; assessment performed outside window, missed assessment, missed visit, PK draw not performed, PK draw performed outside window) that may affect evaluation of PK profile.

Protocol deviations will be listed by participant, treatment, and treatment sequence.

4.3 Demographics/Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment sequence for all participants in the safety population. The demographic and baseline characteristics will consist of age, sex, race, ethnicity, height (cm), weight (kg), body mass index (BMI) (kg/m^2).

All demographic information will be summarized by treatment sequence and overall (across sequences).

Individual demographic and baseline characteristics for the safety population will be listed by participant and treatment sequence.

Age is a calculated parameter. Age will be calculated using the participant's date of birth (date of birth is not included in the database) and the participant's informed consent date.

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, SD, min, median, and max. Number of participants and percentages will be used to describe categorical (discrete) variables (gender, race, and ethnicity).

4.4 General Medical/Surgical History and Procedures/Non-Drug Therapies

Any current medical conditions and/or other significant medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or higher. Any procedures/non-drug therapies that are incurred during the course of the study will also be coded using MedDRA. Medical/surgical history will be listed by subject. Procedures/non-drug therapies will be listed by subject, treatment, and treatment sequence.

4.5 Prior and Concomitant Medications

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

Any medications prohibited in the protocol should not be allowed and will result in the subject being violated by protocol for the PK population. Refer to the protocol for any additional information.

Prior and concomitant medications will be recorded and coded using the current version of WHO Drug Enhanced Dictionary (Global B3 September 2024 or higher). Prior medications will be those that start and end prior to the first dose of study drug. Concomitant medications will be those that have a known end date after the first dose of study drug or have a missing end date. Any concomitant medication taken during the washout period will be assigned to the prior treatment given. Anatomical Therapeutic

Chemical (ATC) classification and Preferred Term will be assigned to each record of prior or concomitant medication. All prior and concomitant medications will be listed by subject and by treatment sequence (both prior and concomitant), and treatment (for concomitant), including ATC classification (level 3), preferred term and reported term, the start and end dates (or ongoing status), dose, unit, frequency, route of drug administration, and indication. All concomitant medications administered will be presented in a data listing.

4.6 Pharmacokinetic Analysis

Pharmacokinetic analyses will be performed for each participant in the PK population. Blood samples will be collected and resulting plasma analyzed to obtain plasma concentrations. The plasma concentration data will be listed at actual and nominal time points by participant. Plasma concentrations will be summarized by treatment at each nominal time point of plasma collection using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max values), and listed by participant, treatment, sequence and with both nominal and actual plasma collection point.

For plasma concentration data, all values below the quantification limit (BQL) will be labeled as such in the concentration listings and treated as zero for the concentration data summary statistics and mean summary figures.

For PK parameter calculations, concentrations BQL will be set to zero if they occur prior to the first quantifiable concentration and after the last quantifiable concentration. The BQL values in between measurable plasma concentrations will be set to missing.

The plasma PK parameters for ARN-75039 will be estimated by non-compartmental analysis (NCA) methods using Phoenix WinNonlin (version 8.1 or higher, Certara USA Inc., Princeton, NJ, USA) and will be based on actual individual time since dosing of blood sample collection.

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

C_{max}	maximum plasma concentration
$C_{min0-24}$	observed plasma concentration from time zero to 24 hours post-dose
t_{max}	time of maximum plasma concentration
λ_z (k_{el})	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 C_{max} and t_{max} will be obtained directly from the experimental observations and AUC_{0-t} will be estimated using the Linear up – Log down trapezoidal method from time 0 hour to last observed concentration hour.

$AUC_{0-\infty}$ will be calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$, where t is the time corresponding to the last measurable plasma concentration (t_{last}). $AUC_{t-\infty}$ is defined as the area under the curve from last measurable concentration estimated to infinity and is calculated by Clast (plasma concentration at the last quantifiable time point) divided by terminal elimination rate constant (Kel). $AUC_{t-\infty}$ will not be an included PK parameter in the listings or tables.

No values for λ (k_{el}), $AUC_{0-\infty}$, CL/F, V_z/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile with at least three timepoints past t_{max} (typically this would be at least the last 3 quantifiable data points representing the terminal elimination phase).

If R-squared adjusted is <0.80, the PK analyst may evaluate whether other time points are more appropriate for the calculation of λ (k_{el}), otherwise λ (k_{el}) and PK parameters derived with λ (k_{el}) such at $t_{1/2}$ and $AUC_{0-\infty}$, will not be reported. R-square adjusted values will be reported in a listing and in the dataset.

For determination of $AUC_{0-\infty}$, if calculated $AUC_{t-\infty}$ is greater than 20% of the calculated AUC from time 0 to infinity, then $AUC_{0-\infty}$ and those PK parameters derived from $AUC_{0-\infty}$ will not be reported. AUC_{inf}% extrapolation values will be reported in a listing and in the dataset.

Pharmacokinetic parameters will be listed by participant, treatment sequence, and treatment for all participants in the PK population. Pharmacokinetic parameters will be summarized by treatment using descriptive statistics descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max values), except for t_{max} which will be described using min, median, and max.

Relative Bioavailability Analysis

The relative bioavailability of ARN-75039 for capsule versus tablet formulation will be evaluated as follows

- Relative Bioavailability of 300 mg ARN-75039 with excipients in tablet form (Treatment B, comparator) versus 300 mg neat ARN-75039 in HPMC capsules (Treatment A, reference product)

For the above comparison confidence intervals (CIs; 90%) will be constructed to test the two one-sided hypotheses at the $\alpha = 0.05$ level of significance for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Natural log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ data will be analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment, period and sequence, and a random effect of subject nested in sequence. This may be an unbalanced model due to possible subject differences between PK parameters reported by treatment.

The relative bioavailability will be established if the 90% CI for the ratio of the population geometric means between comparator and reference product, based on natural log-transformed data, is contained within the equivalence limits of 80.00-125.00% for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (if applicable).

4.7 Safety Analysis

All safety summary tables (as applicable) and listings will be presented.

Safety will be assessed by the incidence of AEs and TEAEs, study discontinuation information, physical examinations, clinical laboratory evaluations, ECGs, and vital signs measurements.

Safety variables will be tabulated (where applicable) and presented for all participants in the safety population. Adverse events will be summarized by MedDRA system organ class, preferred term, and treatment. All safety assessments will be listed.

4.7.1 Study Product Exposure

Exposure to study drug will be listed by participant, treatment sequence, and treatment received, indicating dose date and time. Any deviations will be documented as specified under the Protocol Deviations section and listed separate from the study exposure.

4.7.2 Adverse Events

All AEs occurring during the study, from the signing of informed consent to approximately 7 days following the last study drug administration, including the washout intervals, will be documented on the eCRF. All AEs will be coded and classified according to MedDRA (version 25.1 or higher). Their severity will be graded by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 5.0 or the current version. Adverse events which occur prior to the date and time of the first dose of study drug are considered non-treatment emergent events. Adverse events which occur on or after the date and time of the first dose of study drug up to approximately 7 days following the last drug administration are considered treatment emergent adverse events. Adverse events occurring during a treatment period will be summarized under the treatment received when the AE started. Adverse Events that occur during a washout period will be attributed to the prior treatment.

All treatment emergent AEs (TEAEs) and AEs of special interest (AESIs) will be summarized as the number and percentage of participants by System Organ Class, Preferred Term, and treatment sequence (and overall). Separate summaries will be created by severity and by relationship to study drug. If the same AE (preferred term) is reported more than once for the same participant, it will only be counted once in the summary table. For summary tables by severity and relationship to study drug, if the same AE (preferred term) is reported more than once for the same participant, the highest severity grade (severe > moderate > mild) or the strongest relationship to treatment (related > not related) will be counted in the summary table.

All AEs will be listed, and those that are treatment-emergent will be identified.

All Serious Adverse Events (SAEs) including any deaths will be listed by participants.

All AEs leading to study discontinuation will be listed by participants.

4.7.3 Clinical Laboratory Assessments

Clinical laboratory test parameters (refer to Table 2), with associated reference ranges provided by the laboratory, will be listed for individual participants by treatment sequence and time point. Clinical laboratory test results outside the laboratory's reference ranges will be flagged with "L" for low and "H" for high.

The summary may be produced for blood chemistry and hematology numeric tests only, and would include descriptive statistics for baseline, all post-baseline, and change from baseline values by treatment sequence.

Table 2: Clinical Laboratory Tests

Hematology: • Hematocrit • Hemoglobin • Platelet count • RBC count • WBC count – with differential	**Serum Chemistry**: • Glucose • BUN • Creatinine • Total bilirubin • AST • ALT • GGT • Alkaline phosphatase • Creatine kinase • Total protein • Direct bilirubin • Total bilirubin • Sodium • Potassium • Total CO_2 • Chloride • Calcium • Inorganic phosphate • Magnesium • eGFR
Coagulation: • PT/INR • PTT	
Urinalysis: • Bilirubin • pH • Specific gravity • Protein • Leukocytes • Urobilinogen • Glucose • Nitrates • Ketones • Blood • Microscopic urine analysis	

Urine Drug Screen: • Amphetames • Barbiturates • Opiates • Benzodianes • Cocaine metabolites • Cannabinoids	• Lactate dehydrogenase
Pregnancy Testing: • Serum hCG – at Screening • Urine hCG – at the time of study center admission and Day 15 Discharge or ET	**Post-Menopausal Status Testing:** • FSH • Estradiol
Alcohol Screening: • Breath alcohol test	

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.

4.7.4 Vital Signs Assessments

Vital signs, including systolic (SBP) and diastolic blood pressure (DBP), heart rate, respiration rate, and oral temperature are measured at the time points indicated in the SOA (Table 1). Vital signs (except for height and weight and BMI collected at Screening only) will be monitored periodically during and following study of drug administration. The investigator may repeat the vital signs if deemed appropriate.

All assessments will be listed by participant, treatment sequence, and visit.

A summary table will be produced and will include descriptive statistics for baseline, post-baseline, and change from baseline values by treatment sequence for each vital sign parameter (this will not include BMI which is calculated at screening).

4.7.5 Physical Examinations

A complete physical examination (PE) 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.
A full PE includes assessment of general appearance, skin, HEENT (head, eyes, ears, nose, and throat), neck (including thyroid and nodes), cardiovascular, respiratory, gastrointestinal, and neurological.

Physical examinations may be repeated prior to study discharge as deemed necessary by the Investigator or in response to AE.

Physical examination results will be listed by participant, treatment, and visit.

4.7.6 Electrocardiogram

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 early termination (ET) visit with all measurements taken within 5 minutes apart. 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.

Electrocardiograms may be performed at any time during the study in the interest of subject's safety at the discretion of the Investigator.

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 each day by treatment sequence.

The ECG parameters will be listed by participant, treatment sequence, and visit.

4.8 Interim Analysis

No interim analysis is planned.

4.9 Statistical Programming and Deliverables

All statistical analyses, tables, and listings will be generated in SAS (version 9.4 or later) with appropriate documentation and programming validation. The table of contents of all tables, listings, and figures will be presented in a TLFs shell supplemental document.

4.10 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document (such as the Clinical Study Report), as appropriate.

5 Revision history (for any changes post-Final SAP)

Version	Date	Comments