STATISTICAL ANALYSIS PLAN

VERSION: 3.0

DATE OF PLAN:

10-December-2024

BASED ON:

AT-01B-004 Protocol Amendment 3, 29-MAR-2024

STUDY DRUG:

BEMNIFOSBUVIR (BEM; AT-527) AND RUZASVIR (RZR; AT-038)

PROTOCOL NUMBER:

AT-01B-004

STUDY TITLE:

A PHASE 2, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND EFFICACY OF BEMNIFOSBUVIR (BEM) AND RUZASVIR (RZR) IN SUBJECTS WITH CHRONIC HEPATITIS C VIRUS (HCV) INFECTION

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Sample text is provided in the table below. The list should be tailored to the specific requirements of the protocol and the terminology used in the analysis plan.

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BEM	Bemnifosbuvir
CMH	Cochran Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DAA	Direct-Acting Antiviral
DAIDS	Division of AIDS
DOB	Date of Birth
ET	Early Termination
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
ICD-9	International Classification of Diseases – 9th Edition
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mo	Months
N	Total Sample Size
NIMH	National Institute of Mental Health
OC	Observed Cases
OTC	Over the Counter Medication

Abbreviation	Term
PCR	Polymerase Chain Reaction
RZR	Ruzasvir
SVR4/12/24	Sustained Virologic Response at 4/12/24 weeks post-treatment
PCS	Potential Clinical Significance
EE-PP	Efficacy Evaluable Per-Protocol Population
PC-PP	Pill Compliant Per-Protocol Population
PK/PC-PP	PK and Pill Compliant Per-Protocol Population
RAV	Resistance Associated Variant
s.dSD	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SR	Sustained Release
TEAE	Treatment-Emergent Adverse Event
TG	Treatment Group
TS	Transdermal Delivery System-Placebo
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
VF	Virologic Failure
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol AT-01B-004.

Protocol Revision Chronology:		
Protocol	05-OCT-2022	Original
Amendment 1	09-JAN-2023	An editorial oversight prompted the deletion of "randomized" from the title of the protocol.
Amendment 2	15-AUG-2023	Add/revise language to comply with the European Union Clinical Trial Regulations. Aligns the populations for statistical analyses with the Statistical Analysis Plan and clarifies certain operational issues. Updated the numbers of subjects exposed to bemnifosbuvir and ruzasvir to align with the latest edition of the respective Investigator Brochures. Other minor clarifications.
Amendment 3	29-MAR-2024	Revise the study stopping rules based on feedback from the US FDA. Increases the number of subjects that are permitted to enroll in the optional pharmacokinetic (PK) and pharmacokinetic-viral kinetic (PK-VK) sub-studies. Other minor clarifications.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Lock. Further information can be found in the protocol.

The statistical analysis plan (SAP) is based on:

- Protocol No. AT-01B-004, Amendment 1, dated January 09, 2023
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data for study protocol No. AT-01B-004.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of BEM + RZR
- To evaluate the efficacy of BEM + RZR as assessed by the proportion of subjects achieving SVR12

3.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of BEM + RZR, as assessed by the proportion of subjects experiencing virologic failure (either on-treatment or post-treatment relapse [by 12 weeks post-treatment])
- To evaluate the efficacy of BEM + RZR as assessed by the proportion of subjects achieving SVR24

3.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of baseline RAVs in NS5A and/or NS5B on the efficacy of BEM + RZR
- To evaluate the emergence of NS5A and NS5B RAVs in subjects who experience virologic failure
- To evaluate antiviral activity/viral kinetics (VK) of BEM + RZR
- To evaluate the PK and VK of BEM + RZR in the subgroup of subjects who agree to additional serial PK and VK sampling

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary objectives of this study are:

- To evaluate the safety and tolerability of BEM + RZR
- To evaluate the efficacy of BEM + RZR as assessed by the proportion of subjects achieving SVR12

3.2.2. Secondary Endpoints

Secondary efficacy endpoints include:

- Virologic failure
- SVR24

3.2.3. Exploratory Endpoints

Exploratory endpoints include:

- Resistance to either study drug (BEM or RZR)
- SVR12 in subgroups defined by demographics and/or baseline characteristics
- HCV RNA changes from baseline
- Exposure-response relationships

Refer to Appendix 1 for RNA related derivations.

4. STUDY DESIGN

4.1. Summary of Study Design

AT-01B-004 is an open-label trial to evaluate 8 weeks of treatment with BEM + RZR in subjects with chronic HCV infection. Approximately 280 treatment-naïve subjects with genotype (GT) 1, 2, 3, 4, 5, 6, or 7, either without cirrhosis or with compensated cirrhosis, will be enrolled (Table 2).

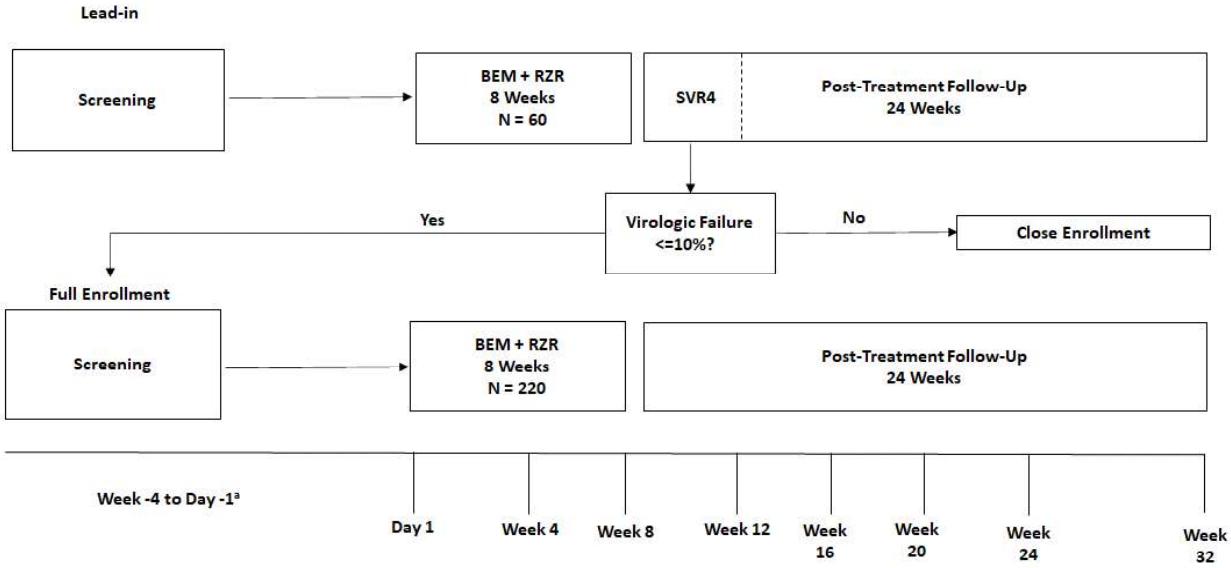
Table 2: Planned Study Enrollment

Total Number	Genotype	Enrollment Targets	Fibrosis Stage
N = 280	1a	n = 75	F0-F4 (Target: 20% with compensated cirrhosis)
	1b	n = 40	
	2	n = 40	
	3	n = 75	
	4	n = 25	
	5, 6, or 7	n = 25	F0-F4 (No specified target for compensated cirrhosis)

A lead-in group of 60 non-cirrhotic subjects will initially be enrolled. At 4 weeks posttreatment, this lead-in group will be evaluated for safety, sustained virologic response at 4 weeks posttreatment (SVR4) and virologic relapse; enrollment will open to the remaining 220 subjects provided that ≤ 6 subjects in the lead-in group (from the Pill-Compliant per-protocol [PC-PP] population) experience virologic failure and no study stopping rules (Protocol Section 5.6) are met.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



[a] Can be extended to 6 weeks under extenuating circumstances with Sponsor approval.
BEM = bemnifosbuvir; RZR = ruzasvir; SVR4 = sustained virologic response at 4 weeks posttreatment

4.2. Definition of Study Drugs

Study drug (550 mg BEM and 180 mg RZR) is to be administered once daily for 8 weeks, i.e., a total of 56 doses. Each dose will be taken as two (2) 275-mg tablets of BEM and two (2) 90-mg capsules of RZR.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

The primary analysis will be based on the PK/PC-PP population. The sponsor expects approximately 95% of the enrolled subjects to meet the PK/PC-PP criteria (Section 6.5.5). Therefore, the PK/PC-PP population is expected to be 71 subjects with GT3 infection, and 266 subjects across all genotypes based on target enrollment provided in Table 3.

Table 3 displays the lower one-sided 95% confidence bounds for a range of potential observed outcomes based on these sample sizes. The table indicates that an observed overall SVR rate in excess of 95% would provide high confidence that the true overall SVR rate is at least 93%. This assumes homogeneity of effect across genotypes. Confidence bounds based on the target genotype 3 enrollment are also presented and these indicate that an observed rate greater than 95% in genotype 3 subjects would provide high confidence that the true SVR rate in genotype 3 subjects is at least 90%.

Table 3: Lower One-sided 95% Confidence Bounds Associated with Observed Outcomes

Observed SVR rate	N=266 evaluable (overall)	N=71 evaluable (GT3 target)[a]
90%	87%	83%
91%	88%	
92%	89%	84%
93%	90%	86%
94%	91%	88%
95%	92%	
96%	93%	90%
97%	95%	92%
98%	96%	

Values are rounded to nearest whole percentage.
[a] Shaded box indicates observed SVR not attainable with N=71.
GT3 = genotype 3; SVR = sustained virologic response

4.3.2. Sample Size Re-Estimation

No sample size re-estimation is planned in this study.

4.4. Randomization

This is an open-label one arm study. No randomization is planned.

4.5. Clinical Assessments

The following assessments will be performed at Screening, with a window for up to 4 weeks prior to the first dose of study drug. This can be extended for up to 6 weeks for extenuating circumstances with sponsor approval.

- Demographics
- Medical history
- Complete physical examination
- Vital signs
- Height and weight
- Triplicate 12-lead ECGs
- Fibrosure (Fibrotest) and APRI, Liver biopsy, FibroScan (if needed)
- Clinical labs and urinalysis

- HBV, HCV, and HIV screen; hemoglobin A_{1c}
- Pregnancy test (females of childbearing potential)
- HCV genotyping
- Viral resistance
- HCV RNA quantitation (PCR)

During the treatment period, viral resistance and HCV RNA PCR samples will be collected corresponding to Day 1, 8, 15, 29, 43, 57, early termination (ET), and follow-up visits (week 4, 12, and 24).

PK samples will be collected corresponding to Day 1 (predose), 8, 15, 29, 43, 57, and ET. In subjects who opt-in for the optional serial PK-only substudy, additional PK samples will be collected on a single occasion during any planned treatment-period visit as early as week 2 at 0.5 (± 15 minutes), 1 (± 15 minutes), 2, 3, 4, 6 and 8 hours postdose (results from the predose PK sample collected as part of the main study will be used as the predose timepoint in the substudy analysis). In subjects who opt-in for the optional serial PK/VK substudy, additional PK/VK (HCV RNA) samples will be collected on Day 1 at 0.5 (± 15 minutes), 1 (± 15 minutes), 2, 3, 4, 6, 8 hours postdose (results of the Day 1 predose PK/VK (HCV RNA) samples collected as part of the main study will be used as the predose timepoint in the substudy analysis), and predose on Days 2 and 3.

Information on study drug administration will be recorded on Day 1, and subjects may be contacted between visits to assess compliance, concomitant medications, and AEs/SAEs.

5. PLANNED ANALYSES

5.1. Interim Analyses

An interim analysis will be performed on data from the lead-in group using the PP population. The proportion of subjects achieving SVR4, defined as HCV RNA < lower limit of quantification [LLOQ] at 4 weeks posttreatment, will be presented with 2-sided 95% confidence intervals (CIs) using the Wilson score method. Virologic failure, defined as either on-treatment failure or posttreatment relapse by 4 weeks posttreatment, will also be estimated and presented with 95% CIs. A virologic failure rate of >10% (> 6 subjects in the lead-in group) will close the study to further enrollment. Safety will also be evaluated, including AEs and clinical laboratory evaluations. The study will also be closed to further enrollment if any study stopping rules are met (Protocol Section 5.6.3).

The interim analysis will include the lead-in group of patients. The interim analysis will be conducted after at least 60 patients have reached their week 4 post-treatment visit or have experienced early VF.

5.2. Final Analyses

The primary analysis will be performed after all participants have completed the assessments for SVR12 or discontinued from the study and all data through 12 weeks post treatment period have been cleaned and finalized.

A Week 24 Follow-up analysis to evaluate the data collected through 24 weeks post treatment period will be performed when all subjects have completed or discontinued from the study and data cleaning has been completed.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Unless otherwise specified, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation (SD), minimum, first quartile, median, third quartile and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as summary statistics.

When a summary tabulates the number of subjects, subjects will only be counted once for a category (e.g., a particular adverse event type, a particular adverse event term, a particular concomitant medication) unless otherwise specified.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

By-subject listings will be sorted by subject ID number, assessment/start date, and assessment/start time (where applicable).

6.3. Data Management

Source documents will be used to record all study-related data. Designated site staff will use the source document entries to enter the data required by the protocol into the eCRFs.

Site staff will be trained on accessing and using the web-based EDC system. Investigational site staff will not be given access to the EDC system until the required training is completed and documented. One eCRF casebook will be completed for each subject enrolled in the study. All source data and eCRFs will be reviewed, evaluated, and signed by the investigator (or designee), as required.

The original source documents and a copy of the corresponding casebook will be retained by the investigator.

Data from eCRFs and other external data (e.g., laboratory data) will be entered into the eCRF or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

In accordance with the vendor’s applicable data management procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual checks and listings. Data queries requiring clarification will be issued in the eCRF and sent to the study site for resolution. Only authorized personnel will make corrections to the clinical data in the eCRF, and all corrections will be documented in an audit trail.

6.4. Data Presentation Conventions

6.5. Analysis Populations

6.5.1. Screened Patients

Screened Patients will include subjects who have signed the study informed consent.

The disposition of these patients will be summarized. For subjects who have failed to meet the inclusion/exclusion criteria reasons for failure will be listed.

6.5.2. Safety Population

The safety population will include all subjects who received at least one dose of the study drug (BEM or RZR).

Efficacy analyses will be performed for this population.

6.5.3. Efficacy Evaluable Per-Protocol (EE-PP) Population

The Efficacy Evaluable population will include subjects who:

1. Met all inclusion/exclusion criteria.
2. Did not receive concomitant medications that are prohibited due to their potential impact on HCV viral load or the pharmacokinetic concentration of either agent (BEM or RZR).
3. Have a collected or imputed (per Table 5) posttreatment viral load assessment at post treatment week 12, unless the subject discontinues early for virologic failure or AE, in which case the ET visit assessment may be used.
4. Has received at least one dose of study drug.

6.5.4. Pill Compliant Per-Protocol (PC-PP) Population

The Per-Protocol Population will include subjects who:

1. Met all inclusion/exclusion criteria.
2. Did not receive concomitant medications that are prohibited due to their potential impact on HCV viral load or the pharmacokinetic concentration of either agent (BEM or RZR).
3. Have a collected or imputed (per Table 5) posttreatment viral load assessment at post treatment week 12 (week 4 for the lead-in analysis), unless the subject discontinues early for virologic failure or AE, in which case the ET visit assessment may be used.
4. Completed treatment, discontinued treatment early due to virological failure, or discontinued treatment early due to drug-related AE.
    - Completed treatment is defined as being in ≥90% compliance with the study drug regimen and was on treatment for a minimum of 51 days. Compliance will be calculated using drug compliance data collected on the eCRF.

The sponsor expects approximately 95% of the enrolled subjects to meet these criteria.

All efficacy analyses will be performed on this population.

6.5.5. PK and Pill Compliant Per-Protocol (PK/PC-PP) Population

The PK Compliant Per-Protocol Population will include subjects who:

1. Met all inclusion/exclusion criteria.
2. Did not receive concomitant medications that are prohibited due to their potential impact on HCV viral load or the pharmacokinetic concentration of either agent (BEM or RZR).
3. Have a collected or imputed (per Table 5) posttreatment viral load assessment at post treatment week 12 (week 4 for lead-in subjects), unless the subject discontinues early for virologic failure or AE, in which case the ET visit assessment may be used.
4. Completed treatment, discontinued treatment early due to virological failure, or discontinued treatment early due to drug-related AE.
    - Completed treatment is defined as being in ≥90% compliance with the study drug regimen. Compliance will be calculated using drug compliance data collected on the eCRF.

      and
    - Adequate exposure corroborated by a Pharmacokinetic Review Committee that is blinded to all other study data. The PK Review Committee will utilize trough PK measurements collected during the dosing period of the study.

All efficacy analyses will be performed on this population.

6.5.6. Pharmacokinetic Populations

The PK population will include all subjects who received at least one dose of both study drugs taken together and for whom evaluable plasma concentration data are available.

The serial PK-only substudy population will include all subjects who received at least one dose of both study drugs taken together and for whom evaluable drug concentration data are available for the visit when serial blood samples were collected.

The serial PK/VK substudy population will include all subjects who received at least one dose of both study drugs taken together and for whom evaluable drug concentration and VK (HCV RNA) data are available for the visit when serial blood samples were collected.

6.6. Baseline Definition

Baseline if defined as the last available assessment prior to first dose of study treatment (BEM and/or RZR).

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Baseline age is the age at the time of enrollment (informed consent date).

6.7.2. Study Day

Study day will be calculated from the first dosing date of study drug (FDD) and derived as follows:

- Assessment date ≥ date of first study drug: Assessment Date – FDD + 1
- Assessment date < date of first study drug: Assessment Date – FDD.

If a subject is enrolled but does not receive any study drug, the enrollment date will be used for reference, in place of FDD.

6.7.3. Change from Baseline

Where applicable, change from baseline will be computed simply as the difference between the post-baseline value and the baseline value.

6.7.4. Visit Windows

For the purposes of by-visit analyses for scheduled clinical assessments (i.e., excluding patient-reported assessments), visit windows for inclusion in the analysis are defined in Table 4. Note that the definition of baseline is provided in Section 6.

Early termination data will be mapped based on the scheduled Study Day of each scheduled visit as specified in the protocol schedule of events.

Visits assigned as "unscheduled" by labs for safety data and HCV RNA quantitation will be mapped based on the table below. If there is more than one unscheduled visit in a visit window, the visit closest to the target date will be used in by-visit analyses. If there is a tie between the number of days from the target date, the later visit will be used. Unscheduled visits that fall within the protocol-defined visit windows will be summarized in the by-visit analyses only if there is no scheduled visit available in the analysis visit window.

Table 4: Visit Windows (Days)

Visit	Relative Target Day	Visit Window (Day)
Screening[a]	-28 - -1	-28 – -1
Baseline/Day 1[b]	1	1
Week 1 (Day 8)	8	2 – 11
Week 2 (Day 15)	15	12 – 21
Week 4 (Day 29)	29	22 – 35
Week 6 (Day 43)	43	36 – 49

Week 8 (Day 57)	57	50 – EOT+20
Post Treatment Week 4	EOT+28	EOT+21 – EOT+69
Post Treatment Week 12	EOT+84	EOT+70 – EOT+146
Post Treatment Week 24	EOT+168	EOT+147 – ≥EOT+210

a. Screening window may be extended to 42 days for extenuating circumstances with Sponsor approval.
b. Day 1 assessment prior to dosing

6.7.5. Multiple Assessments

If multiple assessments are obtained within a visit window for a subject, the value obtained closest to the target timepoint will be used. For any visit, no more than one value per subject will be included in an analysis. In the event of multiple observations that are equidistant form the target day (e.g., two observations on the same day or observations made in a similar time frame before and after target), the earliest value, based on date and time, will be selected.

Multiple efficacy assessments will follow the rules outlined in section 8.7.1.

6.8. Handling of Missing Data

6.8.1. Missing Efficacy Endpoints

Backward imputation will be employed for subjects that do not have a week 4 or week 12 post treatment samples. The imputation will use the nearest post-treatment value that was collected after the missing sample. Missing data that cannot be imputed will be treated as failure.

Forward imputation may be employed for failures as described in Table 5.

Sensitivity analyses will be carried out to evaluate the impact of missing efficacy data.

In the analysis involving the safety population any missing SVR12 that cannot be imputed according to the rules outlined in Table 5 will be considered a failure.

6.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Where the start date for a concomitant medication is missing, the medication will be assumed to have started prior to enrolment in the study. Where the stop date for a concomitant medication is missing, the medication will be assumed to be ongoing to the date of the subject's last assessment.

6.8.3. Missing Start and Stop Dates for Adverse Events

Where the entire start date for an adverse event is missing, the adverse event will be assumed to be treatment emergent. In this case, if the duration of an adverse event is computed, the start date will be considered as the date associated with Day 1. If the month and year of an adverse event is

provided, then the start date will be considered as the later date between the first day of the month/year and the treatment start date.

Where the stop date for an adverse event is missing, the adverse event will be assumed to be ongoing to the date of the subject's last assessment.

7. STUDY POPULATION

7.1. Subjects Disposition

The following will be tabulated (number and percentage) for the screened population:

- Received study drug.
- Did not receive study drug.
- Completed treatment.
- Discontinued treatment, overall and by reason.
- Completed assessment through Post Treatment Week 24.
- Did not complete assessment through Post Treatment Week 24, overall and by reason.

The following will also be tabulated (number and percentage) for the screened population:

- Subjects screened and treated in each country and investigator site.
- Subjects included and excluded (with reason) for each analysis population.

7.2. Screen Failures

The numbers and proportions of subjects who screened but were not treated will be presented as:

- Screen failures
- Subjects who do not have indication of failing to meet I/E criteria but were not treated.

Screen failure reasons will also be tabulated. A subject may have more than one reason for screen failure and all reasons for a subject will be counted, i.e., the sum of subjects across screen failure reasons may exceed the total number of screen failures.

7.3. Protocol Deviations

A final identification and classification of important protocol deviations will be made prior to the freezing of the database and will be documented. The number and percentage of subjects with important protocol deviations and the total number of important protocol deviations by reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized for the enrolled population. A by-subject listing will be provided for those participants with important protocol deviations.

7.4. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented on the enrolled, safety, efficacy evaluable per-protocol, pill compliant per-protocol and pk and pill compliant per-protocol populations.

Demographic variables and baseline characteristics to be summarized may include:

- Age
- Sex

- Race
- Ethnicity
- Region
- Weight
- BMI
- HCV genotype (HCV GT1, GT2, GT3, GT4, GT5, GT6 or GT7)
- Cirrhotic status (non-cirrhotic and compensated cirrhosis)
- Fibrosis stage (F0, F1, F2, F3, and F4)
- HCV RNA quantification (e.g., baseline viral load)
- Prior HCV treatment

7.5. Medical History and Medical Conditions Present at Entry

Complete medical history will be obtained at screening. Medical history records will be coded, using the current version of Medical Dictionary for Regulatory Activities (MedDRA), and summarized by system organ class and preferred term using the safety population.

7.6. Prior Medication History and Medications Present at Entry

Medication will be coded to ATC level 4 using the most recent version of the World Health Organization Drug Dictionary (WHODRUG). Prior medications will be summarized descriptively for the safety population. Prior medications that have been stopped prior to date of first study drug dose will be summarized separately from medications that were started and continued into the study drug treatment period.

A summary of prior medications with indication of HCV will also be provided.

7.6.1. Non-Diagnosis Related Prior Medication History

All medical history data will be listed.

7.6.2. Prior Diagnosis Related Medication History

Enrolled subjects will be DAA treatment naïve, however prior exposure to (peg)interferon with or without ribavirin will be collected and summarized.

7.7. Baseline Physical Examination

A complete physical examination will be performed by a medically qualified individual at baseline. The complete physical examination will include a review of the following: head and neck, ears/nose/throat, lymph nodes, heart, lungs, abdomen, musculoskeletal, neurological, skin, and general appearance.

All clinically significant findings will be recorded as medical history.

7.8. Baseline Vital Signs

Vital sign measurements (body temperature, pulse rate and blood pressure) will be measured at baseline after subjects have had at least 3 minutes of rest. Body weight will be recorded, and BMI will be calculated.

7.9. Baseline Laboratory Data

Laboratory evaluations at baseline will include:

- Serologies for HCV (anti-HCV antibody), HBV (HBsAg), and HIV
- HbA1c
- Hematology: hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count, and mean corpuscular volume
- Coagulation: INR, prothrombin time
- Chemistry: ALT, AST, albumin, alkaline phosphatase, creatine kinase, creatinine, blood urea nitrogen or urea, eGFR calculation (MDRD), total bilirubin (reflex to direct bilirubin), glucose, amylase, lipase, potassium, sodium, bicarbonate, or total carbon dioxide
- Urinalysis: appearance, blood, color, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal
- Serum or urine pregnancy test on females of childbearing potential

7.10. Baseline Primary and Secondary Efficacy Evaluations

Baseline HCV RNA will be quantified, and will be categorized based on greater than or equal to the median as the high-low high cut-off point.

8. EFFICACY

8.1. General Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Analysis of the data from this study will be descriptive in nature. N, mean, standard deviation, first quartile, median, third quartile, minimum, and maximum will be used for continuous data and number and percentage will be used for categorical data, unless specified otherwise.

Mean, median and quartile data will be presented to one decimal place, standard deviation will be presented to two decimal places.

8.2. Timing of Analyses

After the Lead-in group is enrolled and reaches the 4 weeks post-treatment time point, the lead-in group will be evaluated for safety, sustained virologic response at 4 weeks posttreatment (SVR4) and virologic relapse.

Once the enrollment of the main study is completed, and the subjects reach the 12 weeks post treatment (SVR12) the database will be frozen and the primary analysis will be conducted – this primary analysis may serve as the basis for a CSR.

Once all subjects reach the 24 weeks post-treatment, the secondary analyses (i.e. SVR24 related efficacy endpoints and applicable safety after 12 weeks post-treatment) will be conducted. These secondary analyses may be used as the basis for an Addendum to the CSR.

8.3. Testing Statistical Assumptions Including Comparability at Baseline

This is a one arm study. No statistical tests will be performed.

8.4. Statement of the Null and Alternate Hypotheses

No statistical test is planned.

8.5. Subgroup Analyses

Subgroup analysis will be performed according to the following baseline characteristics:

- HCV genotype (HCV GT1, GT2, GT3, GT4, GT5, GT6 or GT7)
- Cirrhotic status (non-cirrhotic, compensated cirrhosis)
- Fibrosis stage (F0, F1, F2, F3, or F4)
- Baseline resistance-associated variants
- Baseline viral load

8.6. Multiple Comparisons and Multiplicity

No statistical tests will be performed; therefore, considerations of multiplicity are not necessary.

8.7. Analysis of the Primary Efficacy Endpoint

8.7.1. Laboratory Result-Based Efficacy Derivations

Efficacy will be determined by HCV RNA results at the relevant timepoints. Each timepoint will have one result for the HCV RNA. In the event that multiple values are present within the window for the timepoint, the latest value will be used. In the event that the timing of duplicate or repeat HCV RNA values is the same, the result with the alphanumerically lowest accession number will be used.

8.7.2. Failure to Achieve Sustained Virologic Response

Subjects may fail to achieve sustained virologic response if they meet virologic failure criteria or for other non-virologic reasons (such as premature discontinuation of study drug or lost to follow-up).

There are two types of virologic failure: on-treatment virologic failure and post-treatment relapse.

8.7.2.1. On-Treatment Virologic Failure

On-treatment virologic failure is defined as any of the following, while on-treatment:

- Not achieving HCV RNA < LLOQ
- Confirmed 1 log10 increase in HCV RNA from post-baseline nadir (would call this "virologic rebound" if we want to name it in parenthesis)
- Confirmed increase in HCV RNA ≥ LLOQ in any subject who achieved HCV RNA < LLOQ

8.7.2.2. Post-Treatment Relapse

Post-Treatment Relapse is defined as HCV RNA ≥ LLOQ after treatment discontinuation in a subject who completed the treatment regimen (at least 51 days) and who had HCV RNA < LLOQ at the time of treatment discontinuation.

Note: Week 8 HCV RNA should be considered "on-treatment" in any subject who received 51 or more days of treatment.

8.7.3. Subjects Receiving Rescue Medications for HCV

Subjects that relapse or fail to achieve SVR and begin non-IP HCV treatment will have failure imputed to timepoints that are subsequent to beginning their non-IP HCV treatment regimen regardless of the observed result HCV viral load results. Imputed timepoints should be excluded from quantitative viral load analyses.

The list of rescue medications is presented in Appendix 2.

8.7.4. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects in the PK and Pill compliant per-protocol population (PK/PC-PP) achieving sustained virologic response at 12 weeks post-treatment (SVR12). Table 5 will be used to derive SVR12 in the analysis populations.

Table 5. Determination of primary outcome (SVR12) for subjects who meet all I/E criteria, did not receive prohibited medications and otherwise met population definition criteria.

On-Treatment Experience	Has 12W Post RNA	Has 24W Post RNA	EOT or W4 Post HCV Positive	Qualifying Result	Primary Outcome
Met Population Specific Criteria	Y			12W Post	12W Post Result
	N	Y		24W Post	24W Post Result
	N	N	Y	Last value	Failure
	N	N	N	NONE	Excluded from population
Early DC for Drug-Related AE	Y				12W Post Result
	N	Y			24W Post Result
	N	N	Y		Failure
	N	N	N		Failure
Early DC for Virologic Failure			Y		Failure
Other					Excluded from population

8.7.5. Sensitivity Analyses of the Primary Efficacy Results

Planned supplemental analyses to support the primary endpoint results include all efficacy analysis for the safety population.

These analyses will be carried out using the same methods as those for the primary efficacy analysis.

8.8. Analysis of the Secondary Efficacy Endpoints

Secondary analysis will include:

- The proportion of subjects in the Efficacy Evaluable and Pill Compliant per-protocol populations (EE-PP and PC-PP) achieving sustained virologic response at 12 weeks post-treatment (SVR12). Table 5 will be used to derive SVR12 in the EE-PP and PC-PP populations.

- The proportion of subjects in the EE-PP, PC-PP and PK/PC-PP populations experiencing virologic failure (on treatment or post-treatment relapse), estimated and presented with 95% CIs using the Wilson score method.
- The proportion of subjects in the EE-PP , PC-PPand PK/PC-PP populations achieving SVR24, analyzed using the same method as for SVR12.

Virologic failure is defined as a confirmed 1 log10 increase in HCV RNA from post-baseline nadir, or confirmed increase in HCV RNA ≥ LLOQ in any subject who achieved HCV RNA < LLOQ.

8.9. Analysis of Exploratory Efficacy Endpoints

Exploratory efficacy analyses for all populations include:

- Proportion of subjects with SVR12 by HCV genotype and presence of baseline NS5A and NS5B RAVs.
- Proportion of subjects with SVR24 by HCV genotype and presence of baseline NS5A and NS5B RAVs.
- Proportion of subjects with SVR4 by HCV genotype and presence of baseline NS5A and NS5B RAVs.
- The proportion of subjects achieving SVR24, analyzed using the same method as for SVR12.
- Proportion of emergence of NS5A and NS5B RAVs in subjects who experience virologic failure. Results will also be summarized by genotype.
- Proportion of baseline NS5A and NS5B RAVs in subjects who experience virologic failure. Results will also be summarized by genotype.
- Prevalence of specific baseline and treatment-emergent NS5A and NS5B RASs by genotype and by virologic failure at SVR12
- SVR12 will be estimated and presented with 95% CIs by demographics and/or baseline characteristics including prior HCV treatment and baseline viral load (baseline viral load will be categorized using the median as a low-high cut-off point).
- HCV RNA IU/ml log10 value will be tabulated by HCV genotype and the average change from baseline over time will be plotted.
- Qualitative HCV RNA results will be tabulated by HCV genotype over time
- Exposure-response relationships will be explored by scatter plots of drug exposure versus change in HCV RNA IU/ml log10 value.

9. SAFETY AND TOLERABILITY

9.1. Overall Summary of Tolerability

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for the safety population. Only treatment-emergent adverse events (TEAE) will be summarized. Treatment emergent adverse events are those with start date/time within the treatment period, defined as the time from first study drug administration to 4 weeks post treatment. Events that occur after 4 weeks with relationship to study drug recorded as 'related' will also be considered as treatment emergent. If the AE onset date is missing or partial, the conventions described in Section **Error! Reference source not found.** will be used to determine if the event is treatment emergent.

Adverse event severity will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

An overall summary of adverse events will be presented and include tabulations (number and %, unless otherwise indicated) for the following:

- Subjects with at least one TEAE, overall and by worst grade
- Total number (number only) of TEAEs
- Deaths
- Subjects who discontinued study due to an AE
- Subjects who discontinued treatment due to an AE
- Subjects with a treatment related AE resulting in treatment discontinuation
- Subjects with a serious adverse event (SAE)
- Subjects with a treatment related SAE
- Subjects with a treatment related AE, overall and by worst grade
- All Adverse Events will be listed

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Adverse events will be coded by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries by SOC and PT will be provided for the following:

- TEAEs
- TEAEs by maximum severity
- Related TEAEs
- TEAEs leading to study discontinuation

- TEAEs leading to treatment discontinuation
- SAEs
- Deaths.

A table of the most common AEs (≥ 5%) will be presented by PT only with display from most common to least.

9.2.1. Summaries of Adverse Events for All Subjects

An overall summary of AEs will be presented including:

- Number of AEs reported
- Number of TEAEs reported
- Number (%) of subjects with at least one TEAE
- Number (%) of subjects with at least one study drug-related TEAEs
- Number (%) of TEAEs by relationship to study treatment
- Number (%) of TEAEs by severity grades
- Number (%) of SAEs
- Number (%) of subjects with a TEAE leading to discontinuation from study drug
- Number (%) of subjects with a TEAE leading to discontinuation from study
- Number (%) of subjects with outcome of death

Frequency tables will be presented:

- Number (%) of subjects with TEAEs by system organ class (SOC) and preferred term (PT)
- Number (%) of subjects with drug-related TEAEs by SOC and PT

9.2.2. Missing and Partial AE Onset Dates

Missing or partial AE start dates will be handled in accordance with section 6.8.3.

9.2.3. Summaries of for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

An overall summary of AEs will be presented including:

- Number of serious AEs (SAEs)
- Number (%) of subjects with at least one SAE
- Number (%) of subjects with at least one study drug-related SAE
- Death and SAEs, if recorded during the study, will be listed.

9.3. Exposure

Study drug exposure will be characterized by the following:

- Number of doses of both study drugs received will be tabulated
- Total amount of both study drugs received will be summarized.
- Number of subjects that are ≥90% compliant/<90% compliant.

9.4. Concomitant and Other Medications

Concomitant medications (CM) are medications that are administered during the treatment-emergent period. If the (CM) onset date and/or end date is missing or partial, the conventions described in Section 6.8.2 will be used to determine if the medication is concomitant. Medications will be presented based on WHODRUG coding.

9.4.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Missing and partial dates for concomitant medications will be handled in accordance with section 6.8.2.

9.5. Routine Laboratory Data

The statistical analysis will present results in standardized units. Continuous laboratory parameters will be summarized by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

Toxicity grades will be presented as cross-tabulations of the toxicity grades at the worse-case analysis visit versus the baseline toxicity. Numbers of subjects with treatment-emergent toxicity grades will also be shown. Shift tables (baseline to worst) will be presented. Laboratory toxicities will be graded according to the DAIDS criteria. Any laboratory abnormalities deemed clinically significant by the investigator will be recorded as Adverse Events.

9.6. Vital Signs

Vital signs parameters will be summarized by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

All vital signs data will be listed.

9.7. Physical Examination

Clinically significant abnormalities detected during the baseline physical examinations will be recorded and presented as Medical History.

Clinically significant abnormalities detected during post-baseline physical examinations will be recorded and presented as Adverse Events.

9.8. ECGs

Descriptive statistics (mean, standard deviation) will be presented for all mean parameter values for the triplicate ECG parameters at every visit. Listings for change from baseline and all ECGs with abnormal interpretation will be created.

9.9. Study Termination Status

The following subject data will be tabulated:

- The number and percentage of subjects who completed or discontinued the study and the number and percentage of subjects for each study discontinuation reason
- The number and percentage of subjects who completed or discontinued the study drug and the number and percentage of subjects for study drug discontinuation reason including Adverse Events leading to study drug discontinuation.

10. PHARMACOKINETICS

10.1. Sparse PK analysis

Sparse PK concentrations will be listed by visit for all subjects with available data.

10.2. Serial PK sub-study

The analysis of the Serial PK sub-study will be discussed in a separate document.

10.3. Serial PK/VK sub-study

The analysis of the Serial PK/VK sub-study will be discussed in a separate document.

11. APPENDICES

11.1. Appendix 1

AT-01B-004 NGS Data Transfer Programming Logic and Table Shells V2.0 20241210

11.2. Appendix 2

AT-01B-004 SAP APPENDIX 2 - Rescue Medications List v1.0 20241028