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

Sponsor Protocol Number:	AT-01B-004
EU CT Number:	2023-504566-28-00
Investigational Products:	Bemnifosbuvir Hemisulfate (BEM; AT-527) and Ruzasvir (RZR; AT-038)
Sponsor	Atea Pharmaceuticals, Inc. 225 Franklin Street, Suite 2100 Boston, MA 02110 +1 (857) 284-8891

COMPLIANCE

The study will be conducted in accordance with this protocol, European Regulation 536/2014, the ethical principles in the latest version of the Declaration of Helsinki, standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

Protocol Version		**Date**
Amendment 3	**FINAL**	**29Mar2024**
Amendment 2	**FINAL**	**15Aug2023**
Amendment 1	**FINAL**	**09Jan2023**
Original	**FINAL**	**06Dec2022**

CONFIDENTIALITY STATEMENT

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STUDY SYNOPSIS

Name of Sponsor/Company: Atea Pharmaceuticals, Inc.		
Name of Investigational Products: bemnifosbuvir hemisulfate (BEM; AT-527) and ruzasvir (RZR; AT-038)		
Protocol Number: AT-01B-004	**Phase:** 2	**Country:** Multiple
Title of Study: 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		

Objectives:

Primary:

- To evaluate the safety and tolerability of BEM + RZR
- To evaluate the efficacy of BEM + RZR as assessed by the proportion of subjects achieving sustained virologic response at 12 weeks post-treatment (SVR12)

Secondary:

- 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 sustained virologic response at 24 weeks post-treatment (SVR24)

Exploratory:

- To evaluate the effect of baseline resistance-associated variants (RAVs) in nonstructural protein (NS) 5A 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 pharmacokinetics (PK) and VK of BEM + RZR in the subgroup of subjects who agree to additional serial PK and VK sampling

Study Design:

This 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.

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 ≤ CCI in the lead-in group experience virologic failure that was not due to poor compliance and no study stopping rules (Section 5.6.3) are met.

Subjects will be screened for up to 4 weeks, although this can be extended for up to 6 weeks for extenuating circumstances with Sponsor approval. Re-screens may be approved on a case-by-case basis by the Sponsor (re-screened subjects will be assigned a new subject number).

Eligible subjects will enter the treatment period and receive BEM + RZR for 8 weeks. After Day 1, during the treatment period, subjects may self-administer study drugs (ie, investigational medicinal product [IMP]) at home, with the exception of subjects who agree to additional blood sampling as part of up to 2 substudies. These subjects will be required to take their study drug in the clinic on certain days (see Table 3).

Subjects will return to the clinic for evaluations at Weeks 1, 2, 4, 6 and 8 (End of Treatment [EOT]) during the treatment period.

Following their last visit of the treatment period (including subjects who prematurely discontinue treatment), subjects will enter the Follow-up period and return to the clinic for evaluations at Follow-up Weeks 4, 12, and 24. End-of-Study (EOS) is defined as the visit at 24 weeks posttreatment.

Adverse events (AEs) and concomitant medications will be reviewed during visits throughout the treatment and follow-up periods. Subjects may also be contacted between visits to assess their compliance with the dosing regimen (during the treatment period) and to discuss AEs and concomitant medications.

The primary endpoint is SVR12. Secondary endpoints include virologic failure and SVR24. Exploratory endpoints are resistance to either study drug (BEM or RZR), SVR12 in subgroups defined by demographics and/or baseline characteristics, HCV RNA changes from baseline and exposure-response relationships. Safety endpoints are the incidence of AEs, serious adverse events (SAEs), and AEs resulting in treatment discontinuation; clinical laboratory abnormalities; vital sign measurements; and electrocardiogram (ECG) parameters.

At clinical sites that agree to participate, there will be two optional substudies (PK only; PK-VK), each requiring separate consent; up to 100 subjects can consent to either or both. Subjects who consent to the PK-only substudy will provide additional blood samples at any planned treatment visit as early as Week 2 based on convenience for subject and investigator. Subjects who consent to the PK-VK substudy will provide additional blood samples a) on Day

1; and b) on Days 2 and 3 (24 and 48 hours after the first dose; ± 2 hours). Study drug will be administered at the clinic on these days (see Table 3).

Number of Subjects Planned:

Approximately 280 subjects will be enrolled, with targets based on GT and compensated cirrhosis status as described in the table below. A blood sample for genotyping will be collected at screening. Genotype results at screening are generally not required to initiate dosing. However, as the study progresses, the Sponsor may use results to help manage these enrollment targets.

A lead-in group of 60 non-cirrhotic subjects will be enrolled and evaluated for SVR4; enrollment will open to the remaining 220 subjects provided that CCI in the lead-in group experience virologic failure that was not due to poor compliance, and no study stopping rules are met (Section 5.6.3). Of the 60 subjects in the lead-in group, a target of 15 GT3-infected subjects will be enrolled; the remainder will be of any GT.

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)

Estimated Duration of Participation:

Subjects will participate in the trial for a maximum of approximately 38 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. The Screening phase is 4 weeks and may be extended to 6 weeks for extenuating circumstances. After Screening, subjects receive treatment for 8 weeks, and are then followed for 24 weeks.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Willing and able to provide written informed consent
2. Male or female subjects between ≥ 18 years of age (or the legal age of consent per local regulations) and ≤ 85 years of age
3. Fridericia-corrected QT (QTcF) interval ≤ 440 ms for males and ≤ 460 ms for females at Screening
   Note: The mean of the triplicate readings, rounded to the nearest whole number, should be used to assess the QTcF.

4. Female subjects of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to the use of an acceptable effective contraception, as described in Section 5.9
5. Females of childbearing potential must have a negative pregnancy test at Screening and at Day 1 prior to dosing
6. Subjects must be direct-acting antiviral (DAA)-treatment-naïve, defined as never exposed to an approved or experimental DAA for HCV
   Note: Prior exposure to (peg)interferon with or without ribavirin is acceptable, as long as it/they were not administered with a DAA.
7. Willingness to provide a blood sample at Screening for genotyping.
8. Documented medical history compatible with chronic HCV, including any one of the following:
   - positive for anti-HCV antibody, HCV RNA, or an HCV GT at least 6 months prior to Day 1, or
   - positive for anti-HCV antibody at Screening with clinical or laboratory evidence of chronic HCV disease, such as the presence of fibrosis by biopsy or noninvasive tests
9. HCV RNA ≥ 1,000 IU/mL at Screening.
10. Liver disease staging assessment as follows:
    - Absence of cirrhosis (F0 to F3) defined as any one of the following:
      – Liver biopsy within 24 months of Day 1 showing absence of cirrhosis
      – Fibroscan® within 12 months of Day 1 with a result of ≤ 12.5 kPa
      – Fibrosure® (Fibrotest®) performed during screening with a score of ≤ 0.48 and an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) of ≤ 1
    - Compensated cirrhosis (F4) defined as any one of the following:
      – Liver biopsy performed prior to Day 1 showing cirrhosis (Metavir stage 4 or equivalent)
      – Fibroscan® within 12 months of Day 1 showing cirrhosis with result > 12.5 kPa
      – Fibrosure® (Fibrotest®) performed during screening with a score of > 0.75 and an APRI of > 2
        APRI formula: AST ÷ lab upper limit of normal (ULN) for AST × 100 ÷ (platelet count ÷ 100).
        NOTE: In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy or Fibroscan® is required. Liver biopsy results supersede the results obtained by Fibroscan® or Fibrosure®.

NOTE: Subjects in the lead-in group must not have F4 cirrhosis.

11. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements

Exclusion Criteria:

1. Female subject is pregnant or breastfeeding
2. Co-infected with hepatitis B virus (HBV; positive for hepatitis B surface antigen [HBsAg]) and/or human immunodeficiency virus (HIV)
3. Abuse of alcohol and/or illicit drug use that could interfere with adherence to study requirements as judged by the investigator
4. Prior exposure to any HCV DAA
5. Requirement of any prohibited medications, as described in Section 5.8
6. Use of other investigational drugs within 30 days of dosing or plans to enroll in another clinical trial of an investigational agent while participating in the present study
7. Subject with known allergy to the study medications or any of their components
8. History or signs of decompensated liver disease: ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or other clinical signs of portal hypertension or hepatic insufficiency
9. Cirrhotic and has a Child-Pugh score >6, corresponding to a Child-Pugh Class B or C
   Note: To calculate the Child-Pugh score, refer to the following website:
   https://www.mdcalc.com/calc/340/child-pugh-score-cirrhosis-mortality
10. History of hepatocellular carcinoma (HCC) or findings suggestive of possible HCC
11. Active clinically significant diseases including:
    - Evidence of history of chronic hepatitis not caused by HCV, including drug-induced hepatitis, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis
    - Cardiac abnormalities/dysfunction that may interfere with subject treatment, assessment, or compliance with the protocol, including unstable angina, unstable congestive heart failure, and unstable arrhythmia
    - Malignant disease or suspicion or history of malignant disease within previous 5 years (except for adequately treated basal or basosquamous cell carcinoma)
    - Any medical condition requiring chronic use of immunosuppressive drugs (e.g., for organ transplantation).
    - Subject with intestinal malabsorption (e.g., structural defects, digestive failure, or enzyme deficiencies, with the exception of lactose intolerance)

- Any other clinically significant medical condition that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results

12. Clinically significant abnormal ECG at Screening, as determined by the investigator.
13. Any of the following laboratory parameters at Screening:
    - Alanine aminotransferase (ALT) or AST > 10 x ULN
    - Total bilirubin > 3 mg/dL (> 51.3 µmol/L)
    - Albumin < 2.8 g/dL (< 28 g/L)
    - International Normalized Ratio (INR) > 2.2 unless subject has a stable INR on an anticoagulant
    - Hemoglobin < 10 g/dL
    - Hemoglobin A_{1c} (HbA_{1c}) > 8.5%
    - Platelet count < 50 x 10^9/L
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease (MDRD) formula
    - Concomitant grade ≥2 toxicity of both lipase and amylase per Division of AIDS criteria (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

      Note: Retests of Screening laboratory parameters or assessments may be permitted once in certain scenarios with medical monitor approval. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting Screening laboratory results.

Investigational Product, Dosage, and Mode of Administration:

- BEM (manufactured by CCI [redacted] or CCI [redacted].) will be provided as 275-mg tablets (A2-275 mg tablets)
- RZR (manufactured by CCI [redacted]) will be provided as 90-mg capsules
- Subjects will take 550 mg BEM (as 2 x 275-mg tablets) and 180 mg RZR (as 2 x 90-mg capsules) once daily for 8 weeks
- Study drugs will be taken together orally
- Subjects will be instructed to take the study drugs in the morning at approximately the same time each day. Study drugs can be taken with water and with or without food.

Duration of Treatment:

The duration of treatment will be 8 weeks.
Reference Therapy, Dosage, and Mode of Administration: Not applicable
Criteria for Efficacy SVR12 and SVR24 are defined as HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] at 12 weeks and 24 weeks respectively post-treatment.
Statistical Methods: Results of all efficacy analyses will be presented by genotype and cirrhotic status. All efficacy analyses will be performed on the PP population(s) consisting of all subjects who: • Meet all inclusion/exclusion criteria • Do 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). • Have a collected or imputed posttreatment viral load assessment at posttreatment Week 12 (posttreatment Week 4 for lead-in subjects) unless the subject discontinues early for virologic failure or AE, in which case the ET visit may be used • Complete treatment (≥90% compliance with the study drug regimen), discontinue treatment early due to virological failure or discontinue treatment early due to a drug-related AE *Note: 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. An interim analysis will be performed on data from the lead-in group using the PP population(s). The proportion of subjects achieving SVR4, defined as HCV RNA < 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% that is not due to poor compliance (> CCI [redacted] in the lead-in group) will close the study to further enrollment. Safety will also be evaluated, including AEs and clinical laboratory evaluations. The primary efficacy endpoint is SVR12. The proportion of subjects achieving SVR12 with two-sided 95% CIs using the Wilson score method will be presented. Reasons for failure to achieve SVR12 will be summarized. Secondary efficacy endpoints and corresponding analyses include:

- The proportion of subjects in the PP population(s) experiencing virological failure (either on-treatment or post-treatment relapse by 12 weeks post treatment) will be estimated and presented with 95% CIs.
- The proportion of subjects in the PP population(s) achieving SVR24 will be analyzed using the same method as SVR12.

All subjects who receive at least one dose of either study drug will be included in the safety analyses.

Study treatment exposure (such as treatment duration and total dose received) will be summarized with descriptive statistics.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of subjects with treatment-emergent adverse events will be tabulated by primary System Organ Class and Preferred Term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug.

Changes from baseline in laboratory tests and vital signs will be summarized. Laboratory abnormalities will be graded in accordance with the Division of AIDS (DAIDS) severity scale, where applicable. Shift tables for treatment-emergent laboratory abnormalities will be presented.

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. Plasma concentrations of the study drugs and metabolites will be listed by time point and summarized using descriptive statistics, as applicable.

The 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 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. Derived PK parameters (e.g., maximum observed plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) will be summarized descriptively.

LIST OF ABBREVIATIONS

Term	Definition
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase-to-platelet ratio index
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from time 0 to the last time point (ie, corresponding to a quantifiable concentration)
BEM	Bemnifosbuvir
BMI	Body mass index
CI(s)	Confidence interval(s)
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
DAA(s)	Direct acting antiviral(a)
DAIDS	Division of AIDS
DDI	Drug-drug interaction
$EC_{50/95}$	50% effective concentration
ECG	Electrocardiogram(s)
eCRF	Electronic case report form
EDC	Electronic Data Capture
E_{max}	Maximal effect
EOS	End of Study, defined as the day in which the subject completes their last assessment; the planned EOS is study Week 32 (i.e., 24 weeks posttreatment)
EOT	End of Treatment, defined as the last day study drug is administered; the planned EOT is at the end of Week 8
ET	Early termination
EU	European Union
FDC	Fixed-dose combination
GCP	Good Clinical Practices
(e)GFR	(Estimated) Glomerular filtration rate
GT	Genotype
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
LLOQ	(Lower) Limit of quantitation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
NS	Nonstructural
NS5A	Nonstructural protein 5A
NS5B	Nonstructural protein 5B
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Preferred term / Prothrombin time
QTcF	Fridericia-corrected QT interval
RAV(s)	Resistance-associated variant(s)
RBC	Red blood cell
RZR	Ruzasvir
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SVR4/12/24	Sustained virologic response at 4/12/24 weeks posttreatment
ULN	Upper limit normal
UPR	uprifosbuvir
VK	Viral kinetics

PRINCIPAL INVESTIGATOR PROTOCOL APPROVAL

Protocol Number: *AT-01B-004*

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

I have read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

_____ _____

Signature Date (dd-mmm-yyyy)

Principal Investigator

_____

Printed Name

Principal Investigator

1. INTRODUCTION

1.1. Background

There are approximately 58 million people globally who are chronically infected with hepatitis C virus (HCV), with about 1.5 million new infections occurring per year. A significant number of those with chronic infection will go on to develop cirrhosis, hepatocellular carcinoma, or liver failure, resulting in approximately 290,000 deaths each year [1]. Despite the significant advances in treatment, HCV remains a global health burden largely owing to the epidemic of injection drug use, and a lack of diagnosis of many of those who have been infected. The number of acute HCV cases reported in the US has increased every year during 2012–2019, with the highest rates in persons aged 20–39 years, consistent with age groups most impacted by the nation's opioid crisis[2]. Similar trends have been observed in the European Union (EU). Although improving, global access to HCV treatments also remains limited. Of the 58 million living with HCV infection globally in 2019, an estimated 9.4 million (16%) persons had been treated with direct-acting antivirals (DAAs) by the end of 2019 [1].

Oral DAAs have drastically improved efficacy outcomes, with much improved safety profiles compared to the interferon-containing regimens of the past. Sustained virologic response (SVR) rates with oral DAA regimens (e.g., EPCLUSA®, HARVONI®, MAVYRET™), are generally greater than 95%, with treatment durations of 8-12 weeks for most patients, depending on the regimen and patient population [3,4,5]. The more difficult-to-treat patient populations include those with HCV genotype (GT) 3 infection, prior DAA treatment failure, or cirrhosis. Depending on regimen (e.g., EPCLUSA/HARVONI), some of these populations require at least 12 weeks of treatment and still with adjunctive ribavirin dosing (for patients with decompensated cirrhosis). Furthermore, none of the approved HCV protease inhibitor-containing regimens (eg, MAVYRET) are indicated in patients with decompensated cirrhosis. An ideal novel regimen would have high efficacy with a simple 8-week or shorter treatment duration in broad patient populations, with improved safety (compared to protease inhibitor and ribavirin-containing regimens), and less drug-drug interaction potential compared to currently approved regimens.

Atea Pharmaceuticals, Inc. is developing a novel, oral two-drug combination regimen for the treatment of chronic HCV infection. The two drugs in the regimen are bemnifosbuvir hemisulfate (referred to as bemnifosbuvir, BEM) and ruzasvir (referred to as RZR or AT-038, formerly known as MK-8408). BEM is a unique 6-modified purine nucleotide prodrug and RZR is a small molecule nonstructural protein 5A (NS5A) inhibitor of HCV.

BEM is a hemisulfate salt of AT-511, a phosphoramidate protide that is converted after multi-step activation to the active 5'-triphosphate metabolite (AT-9010). AT-9010 is a potent inhibitor of the HCV nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase after incorporation into HCV RNA, causing termination of chain elongation. AT-511 exhibited potent pan-genotypic anti-HCV activity in replicons containing NS5B sequences derived from laboratory reference strains of GT1a-5a, with 50% effective concentration (EC_{50}) values ranging from 9 to 28 nM and having 6- to 11-fold greater intra-assay potency than sofosbuvir. Similarly, AT-511 showed potent pan-genotypic anti-HCV activity in replicons containing NS5B sequences from clinical isolates (GT1a-4d), with EC_{50} and 95% effective concentration values

ranging from 6 to 14 nM and 33 to 80 nM, respectively, which were 4- to 14-fold more potent than sofosbuvir. A comprehensive nonclinical development program has fully characterized the nonclinical pharmacology, pharmacokinetics and metabolism, and nonclinical toxicology of BEM. BEM has a clean nonclinical safety profile, with no target organs of toxicity identified in toxicology studies up to 13 weeks in duration, no evidence for genetic toxicity, no concerning findings in developmental and reproductive toxicology studies, and no test-article related findings in safety pharmacology studies. In the Phase 1 clinical study AT-01B-001 (N=88), healthy or HCV-infected subjects received either single or multiple doses (seven daily doses) up to 600 mg BEM (equivalent to 553 mg AT-511 free base). Rapid and potent pan-genotypic antiviral activity was observed with BEM, regardless of cirrhosis status. Mean maximum HCV RNA reductions of 4.4 $\log_{10}$ IU/mL after 7 days of dosing with BEM (553 mg free base) were observed in non-cirrhotic GT1 HCV-infected subjects. Similar potent antiviral activity was also observed in both non-cirrhotic GT3 and Child-Pugh A cirrhotic HCV-infected subjects, with mean maximum HCV RNA reductions of 4.5 $\log_{10}$ IU/mL and 4.6 $\log_{10}$ IU/mL, respectively, after 7 days of dosing with BEM (553 mg free base). Pharmacokinetic-pharmacodynamic (PK-PD) analysis indicated that antiviral activity closely correlated with plasma exposure of AT-273. Maximal effect (E_{max}) modeling demonstrated that BEM doses of 550 mg free base will result in maximal viral load reduction. In the Phase 2 study AT-01B-002 (N=10), daily treatment with 550 mg BEM and 60 mg daclatasvir was evaluated for durations of 8 to 12 weeks. Despite the use of a less potent first-generation HCV NS5A inhibitor, viral load decreased rapidly, with 70% of subjects achieving plasma HCV RNA < lower limit of quantitation (LLOQ) by Week 2 (and 50% achieving target not detected by Week 2). Eight of the 9 subjects who received 8 weeks of treatment went on to achieve sustained virologic response at 12 weeks posttreatment (SVR12), and the single subject who received 12 weeks of treatment also achieved SVR12. The very rapid early clearance of HCV RNA observed in this study supports continued evaluation of BEM with a more potent, next-generation HCV NS5A inhibitor. In addition, this study provided proof-of-concept that a drug combination including BEM (albeit with a first-generation NS5A inhibitor) could result in SVR12 with 8 weeks of treatment. In the HCV program, BEM doses up to 550 mg daily have been well tolerated for durations up to 8-12 weeks. Adverse events (AEs) were generally mild or moderate in intensity, with no clinically relevant patterns in laboratory, electrocardiogram (ECG), or vital signs parameters. Additional details on the clinical and non-clinical studies are described in the BEM Investigator's Brochure.

RZR was initially developed for HCV by Merck and has since been licensed by Atea after CCI [redacted] with 292 subjects who received doses of RZR as a single-drug formulation, 225 subjects who received RZR as part of a fixed-dose combination in Phase 1 studies, and 1269 HCV GT1-6-infected subjects who had received daily RZR doses of 60 or 180 mg for 8 to 24 weeks in Phase 2 studies as part of 2-drug and 3-drug regimens. RZR has broad, potent pan-genotypic activity with an $EC_{50} \leq 10$ pM against subgenomic replicons from GT1-6. RZR retains its potent activity in full-length infectious viruses from GT1a (H77Sv3) and GT2a (JFH-1) as well as against GT1a resistance-associated variants (RAVs) selected by previous NS5A inhibitors in the clinic. Its potency is also not affected by signature RAVs from other HCV DAA classes. In combination with other DAAs, additive to synergistic antiviral effects were observed *in vitro*. Synergy experiments conducted *in vitro* by Atea in HCV GT1b replicon (Huh-luc/neo-

ET) cells demonstrate a synergistic antiviral effect between RZR and BEM. Results of the nonclinical safety program have demonstrated an acceptable safety profile that compares favorably to other HCV NS5A protein inhibitors and supports the continued clinical development of RZR. Collectively, the battery of *in vitro* and *in vivo* genetic toxicity studies, safety pharmacology and phototoxicity studies, pivotal Good Laboratory Practice repeat-dose oral toxicity studies in rats up to 6 months, including a 1-month combination toxicity study in rats with uprifosbuvir (UPR; a nucleoside prodrug inhibitor of HCV NS5B previously developed by Merck) and dogs up to 9 months revealed minimal non-adverse findings. A 13-week combination toxicity study in rats with BEM has also been conducted, and preliminary results indicate that the combination of RZR at 500 mg/kg/day and BEM at 500 mg/kg/day is well tolerated. Pharmacodynamic data from a Phase 1b proof-of-concept study in HCV-infected patients (MK-8408-003) demonstrated RZR monotherapy for 5 days achieved viral load reduction (> 3 $\log_{10}$ reductions) in HCV GT1-, 2- and 3-infected patients, supporting evaluation of RZR at a dose equal or greater than 10 mg in combination with other antiviral agents. Prior Phase 2 studies conducted by Merck evaluated the 2-drug combination regimen of RZR (60 mg and 180 mg) + UPR (450 mg) once daily for 12 weeks in cirrhotic or non-cirrhotic subjects infected with HCV GT1-6. While high SVR12 rates (>90%) were observed at both doses of RZR in GT1-6-infected subjects overall and who were noncirrhotic, CCI [redacted]

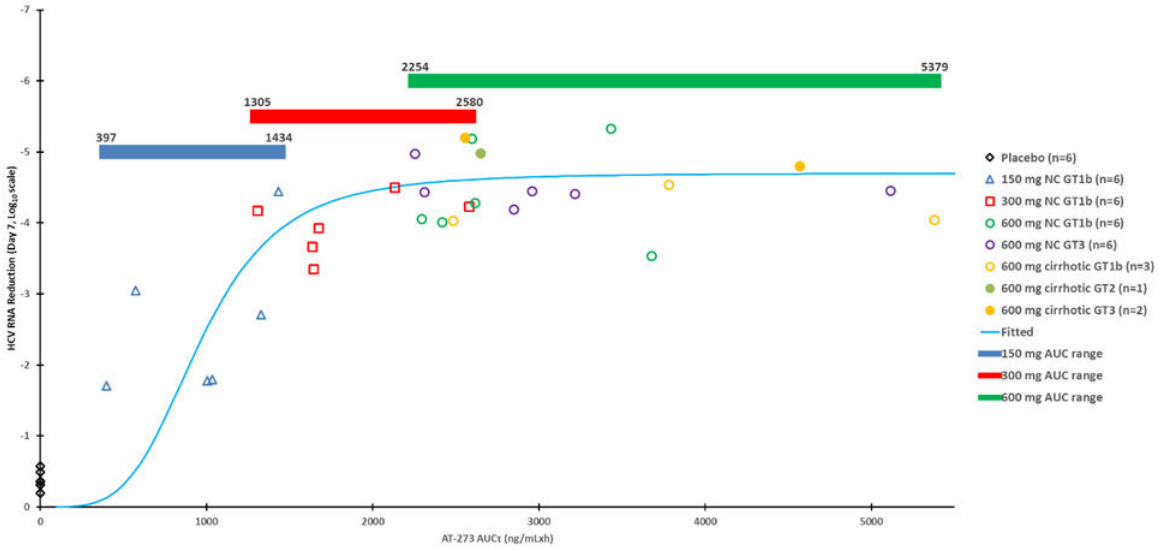
Additional details on the clinical and non-clinical studies are described in the RZR Investigator's Brochure.

1.2. Rationale for the Dose Selection

1.2.1. BEM

A 550 mg daily dose of BEM was selected as the optimal dose for evaluation in this study. As described in the BEM Investigator's Brochure, a standard E_{max} model was used to support this dose selection. As presented in Figure 1, the fitted curve indicates that E_{max} is achieved with AT-273 (guanosine nucleoside metabolite representing intracellular active triphosphate) area under the plasma concentration-time curve from time 0 to the last time point (AUC_{τ}) greater than 2000 ng/mL*h. Only the 600 mg/day dose of BEM (553 mg AT-511 free base equivalent) produced AT-273 AUC_{τ} values that are consistently above the threshold of 2000 ng/mL*h.

Figure 1: Exposure-Response Analysis (Study AT-01B-001)



In addition, as summarized in the BEM Investigator's Brochure, the steady-state exposures of BEM and its metabolites achieved at the no-observed-adverse-effect level doses in the 13-week toxicology studies exceeded the steady-state exposures observed in humans, providing adequate exposure multiples for a daily dose of 550 mg. BEM doses at 550 mg daily have been well tolerated at durations of up to 8-12 weeks.

1.2.2. RZR

A daily dose of 180 mg RZR was selected as the optimal dose for evaluation in this study. As described in Section 1.1, prior Phase 2 studies conducted by Merck evaluated both 60 mg and 180 mg daily doses of RZR as part of a 2-drug combination regimen with UPR. CCI [redacted]

At the 180-mg dose of RZR, the target area under the concentration time curve over 24 hours ($AUC_{0\text{-}24h}$) is 233 uM•h. Based on the animal-to-human $AUC_{0\text{-}24h}$, the safety exposure multiples in rats at the end of 1 and 6 months of daily dosing, and in dogs at the end of 9 months of daily dosing, were 6-fold and 50-fold respectively, relative to this target. These data support the safety of RZR.

Furthermore, RZR has been generally well-tolerated in HCV-infected patients when administered as once daily doses of 180 mg (282 subjects) for up to 12 weeks combined with UPR alone or at a daily dose of 60 mg (936 subjects) for 8 to 24 weeks in combination with UPR and grazoprevir. There were no observed cardiac or renal safety signals. Drug-related serious

adverse events (SAEs) and drug-related discontinuations due to AEs were rare. There were no consistent treatment-related changes in labs, vital signs, or ECG safety parameter values.

1.3. Study Rationale

A combination of BEM and RZR has the potential to provide a convenient, protease-sparing, pan-genotypic treatment regimen for HCV-infected patients with or without cirrhosis. This Phase 2 study is designed to compare the efficacy and safety of this combination therapy after 8 weeks of treatment. The results of this study will support future later phase studies of BEM and RZR.

1.4. Risk/Benefit Assessment

The non-clinical and clinical data summarized in the respective Investigator's Brochures indicate an encouraging risk-benefit profile for BEM and RZR, supporting advancement of the combination to Phase 2 clinical trials with an expectation of clinical safety and marked anti-HCV efficacy.

Over 750 human subjects have been exposed to BEM across both Coronavirus Disease 2019 (COVID-19) and HCV development programs. There have been no deaths in subjects receiving BEM, and none of the reported SAEs in the BEM program have been related to study drug (ie, investigational medicinal product [IMP]; SAEs have only been reported in the COVID-19 program). Gastrointestinal-related AEs, specifically mild to moderate nausea and vomiting, have been observed more frequently at BEM doses > 550 mg twice daily (reported in the COVID-19 program), however, tolerability at lower doses including the HCV dose of 550 mg daily has been comparable to placebo. In the AT-01B-002 Phase 2 study, BEM was evaluated in combination with a first-generation NS5A inhibitor (daclatasvir) in HCV-infected subjects for durations of up to 8 weeks (9 subjects) and 12 weeks (1 subject) with no safety issues. This study also provided proof-of-concept that a drug combination including BEM (albeit with a less potent NS5A inhibitor) could result in SVR12 with 8 weeks of treatment. There have been no clinically significant patterns in laboratory parameters or ECGs in the BEM program.

Similarly, RZR has been evaluated in over 1800 human subjects, including 1269 HCV-infected subjects where RZR was administered as part of 2 and 3 drug combination regimens (including a nucleoside analog and protease inhibitor). In a prior Phase 2 study in 282 HCV-infected subjects, a daily dose of 180 mg combined with UPR was well tolerated for 12 weeks.

For both compounds, there has been no evidence for genetic toxicity, no concerning findings in developmental and reproductive toxicology studies, and no test-article related findings in safety pharmacology studies. Although there is substantial precedent for drug combinations including nucleoside analogs and NS5A inhibitors for the treatment of HCV, a 13-week combination toxicity study in rats with BEM and RZR has also been conducted, and preliminary results indicate that the combination is well tolerated.

The present protocol mandates thorough clinical and laboratory safety monitoring, with routine testing. Standard serum chemistries, complete blood counts with differentials, urinalyses and clinical AEs will also be monitored. In addition, safety-related stopping rules for individuals (Section 5.6.2) and the study (Section 5.6.3) have been incorporated into the protocol to further reduce subject risk.

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation. However, the potential benefit to subjects is that the combination regimen is reasonably anticipated to be a curative regimen for their HCV infection. The likelihood of rapid HCV RNA clearance to non-detectable levels which can potentially result in SVR achievement is supported by the potent pan-genotypic anti-HCV activity observed in non-clinical virology studies and the clinical studies conducted to date (summarized in Section 1.1). Both compounds have potent pan-genotypic activity and have demonstrated SVR in the clinic in differing combination regimens. For BEM, SVR12 has been observed in HCV-infected subjects after 8 weeks of treatment with a less potent, first-generation NS5A inhibitor (daclatasvir). Furthermore, antiviral activity of BEM after monotherapy was not diminished in GT3-infected subjects or those with compensated cirrhosis, populations which are generally more difficult to treat. Combining BEM with a more potent NS5A inhibitor such a RZR is anticipated to result high rates of SVR12 after 8 weeks of treatment. Therapy with any DAA has the potential to select for the emergence of drug-resistant viral mutants. However, consistent with its high pan-genotypic potency *in vitro*, and its retained activity against prototype nucleoside-resistant mutants, BEM is expected to have a high resistance barrier in HCV-infected patients. RZR retains its potent activity against GT1a RAVs selected by previous NS5A inhibitors in the clinic. Its potency is also not affected by signature RAVs from other HCV DAA classes. The emergence of resistance will be evaluated in this study.

As study AT-01B-004 is designed to explore 8 weeks of treatment, a lead-in group of 60 subjects (non-cirrhotic male and female) will be initially enrolled and treated. Atea will evaluate safety and the rate of sustained virologic response at 4 weeks posttreatment (SVR4) in the lead-in group before enrollment is fully opened. To mitigate the risk of treatment failures, enrollment will only open to the remaining 220 subjects provided that CCI in the lead-in group experience virologic failure that was not due to poor compliance, and that no study stopping rules are met (Section 5.6.3). Additional protocol-defined virologic stopping rules (Section 5.6.1) are also incorporated to immediately discontinue subjects not responding to treatment. For those subjects who generally comply with the study protocol and experience lack of efficacy (failure to achieve SVR12 or sustained virologic response at 24 weeks posttreatment [SVR24]) with the investigational regimen, the Sponsor may reimburse the investigator for the cost of a course of post-study medication depending on local drug access and reimbursement policies.

These considerations support a favorable risk/benefit profile for evaluation of BEM and RZR in this study.

2. STUDY OBJECTIVES

2.1. 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

2.2. 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

2.3. Exploratory Objectives

- 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

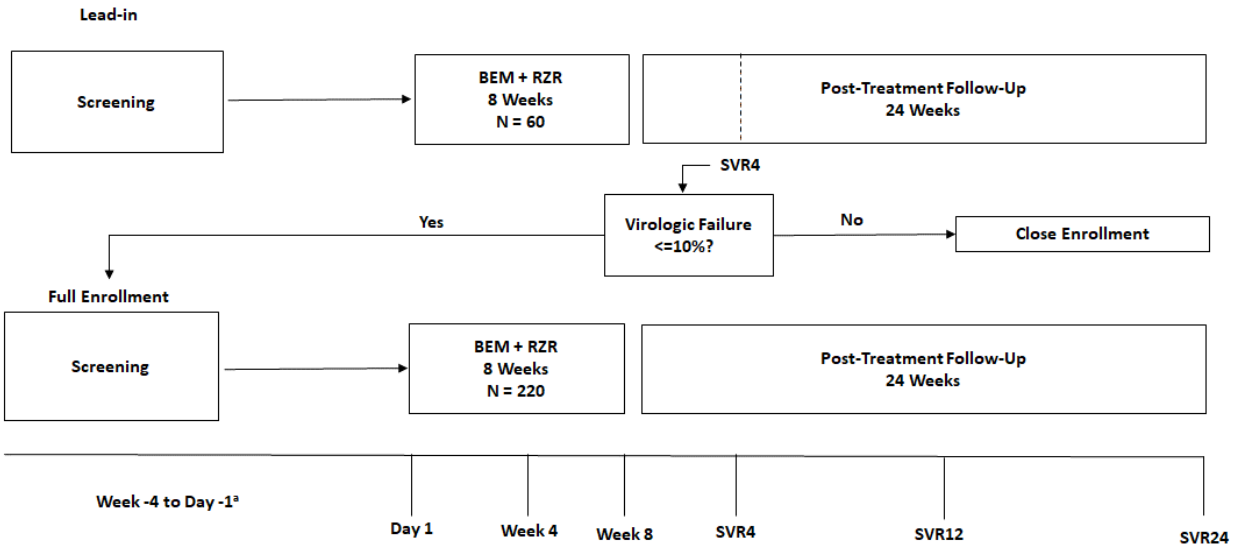
3. STUDY DESIGN

3.1. General Study Design

This is an open-label trial to evaluate 8 weeks of treatment with BEM + RZR in subjects with chronic HCV infection (Figure 2). 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.

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, SVR4, and virologic relapse; enrollment will open to the remaining 220 subjects provided that CCI in the lead-in group experience virologic failure that was not due to poor compliance and no study stopping rules are met (Section 5.6.3).

Figure 2: 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

Subjects will be screened for up to 4 weeks, although this can be extended for up to 6 weeks for extenuating circumstances with Sponsor approval. Such circumstances may include awaiting reporting of laboratory results or scheduling assessment of cirrhosis (eg, FibroScan®) if needed. Re-screens may be approved on a case-by-case basis by the Sponsor (re-screened subjects will be assigned a new subject number).

At the end of the screening period (Baseline; Day 1), eligible subjects will enter the treatment period and receive BEM + RZR for 8 weeks. After Day 1 during the treatment period, subjects

may self-administer study drugs (ie, IMP) at home, with the exception of subjects who agree to additional PK and/or PK-VK blood sampling as part of up to two substudies. These subjects will be required to take their study drug in the clinic on certain days (see Table 3).

Subjects will return to the clinic for evaluations at Weeks 1, 2, 4, 6, and 8 (End of Treatment [EOT]) during the treatment period.

Following their last visit of the treatment period (including subjects who prematurely discontinue treatment) subjects will enter the Follow-up period and return to the clinic for evaluations at Follow-up Weeks 4, 12, and 24. End-of-Study (EOS) is defined as the visit at 24 weeks posttreatment.

Adverse events and concomitant medications will be reviewed during visits throughout the treatment and follow-up periods. Subjects may also be contacted between visits to assess their compliance with the dosing regimen (during the treatment period) and to discuss AEs and concomitant medications.

The primary endpoint is SVR12. Secondary endpoints include virologic failure and SVR24. Exploratory endpoints are resistance to either study drug (BEM or RZR), SVR12 in subgroups defined by demographics and/or baseline characteristics, HCV RNA changes from baseline and exposure-response relationships. Safety endpoints are the incidence of AEs, SAEs, and AEs resulting in treatment discontinuation; clinical laboratory abnormalities; vital sign measurements; and ECG parameters.

At clinical sites that agree to participate, there will be two optional substudies (PK only; PK-VK), each requiring separate consent; up to 100 subjects can consent to either or both. Subjects who consent to the PK-only substudy will provide additional blood samples at any planned treatment visit as early as Week 2 based on convenience for subject and investigator. Subjects who consent to the PK-VK substudy will provide additional blood samples a) on Day 1; and b) on Days 2 and 3 (24 and 48 hours after the first dose; ± 2 hours). Study drug will be administered at the clinic on these days (see Table 3).

Patients with HCV or HCV patient groups were not consulted. The study conforms to many aspects of canonical HCV study design and patient care, as described in both health authority guidance [6] and clinical practice guidelines [7].

This is a global clinical trial that complies with the European Union Clinical Trial Regulations. Results will be released to a publicly accessible web site (eg, Clinical Trial Information System [CTIS]) after the last European subject's completion of the study. However, if the study is ongoing outside the EU as of that date, results will be released after the last subject's completion date.

3.2. Number of Subjects

Approximately 280 subjects will be enrolled, with targets based on GT and compensated cirrhosis status (Table 1). A blood sample for genotyping will be collected at screening. Genotype results at screening are generally not required to initiate dosing. However, as the study progresses, the Sponsor may use results to help manage these enrollment targets.

A lead-in group of 60 non-cirrhotic subjects will be enrolled and evaluated for SVR4; enrollment will open to the remaining 220 subjects provided that CCI in the lead-in group experience virologic failure that was not due to poor compliance, and no study stopping rules are met (Section 5.6.3). Of the 60 subjects in the lead-in group, a target of 15 GT3-infected subjects will be enrolled; the remainder will be of any GT.

Table 1: 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)

4. SUBJECT SELECTION

4.1. Study Population

Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for participation in this study. A signed copy of the informed consent form will be provided to each subject.

Both eligible males and females between 18 and 85 (inclusive) years of age will be enrolled in the study. HCV disproportionately affects more men than women, and prevalence is higher in people over 50 years. However, in people who inject drugs or engage in behaviors that increase the risk of transmitting bloodborne diseases, the risk for acquiring HCV is elevated regardless of sex or age. As such, including both males and females across the adult lifespan ensures that enrolled subjects represent the diversity of the patient population. In addition, current nonclinical data supports enrolling females of childbearing potential and male subjects with childbearing-potential partners provided acceptable effective contraception is used, as specified in Section 5.9.

4.2. Inclusion Criteria

1. Willing and able to provide written informed consent
2. Male or female subjects between ≥ 18 years of age (or the legal age of consent per local regulations) and ≤ 85 years of age
3. Fridericia-corrected QT (QTcF) interval ≤ 440 ms for males and ≤ 460 ms for females at Screening
   Note: The mean of the triplicate readings, rounded to the nearest whole number, should be used to assess the QTcF.
4. Female subjects of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to the use of an acceptable effective contraception, as described in Section 5.9
5. Females of childbearing potential must have a negative pregnancy test at Screening and at Day 1 prior to dosing
6. Subjects must be DAA-treatment-naïve, defined as never exposed to an approved or experimental DAA for HCV
   Note: Prior exposure to (peg)interferon with or without ribavirin is acceptable, as long as it/they were not administered with a DAA.
7. Willingness to provide a blood sample at Screening for genotyping.
8. Documented medical history compatible with chronic HCV, including any one of the following:
   a. positive for anti-HCV antibody, HCV RNA, or an HCV GT at least 6 months prior to Day 1, or
   b. positive for anti-HCV antibody at Screening with clinical or laboratory evidence of chronic HCV disease, such as the presence of fibrosis by biopsy or noninvasive tests

9. HCV RNA ≥ 1,000 IU/mL at Screening.
10. Liver disease staging assessment as follows:
    - Absence of cirrhosis (F0 to F3) defined as any one of the following:
      - Liver biopsy within 24 months of Day 1 showing absence of cirrhosis
      - Fibroscan® within 12 months of Day 1 with a result of ≤ 12.5 kPa
      - Fibrosure® (Fibrotest®) performed during screening with a score of ≤ 0.48 and an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) of ≤ 1
    - Compensated cirrhosis (F4) defined as any one of the following:
      - Liver biopsy performed prior to Day 1 showing cirrhosis (Metavir stage 4 or equivalent)
      - Fibroscan® within 12 months of Day 1 showing cirrhosis with result > 12.5 kPa
      - Fibrosure® (Fibrotest®) performed during screening with a score of > 0.75 and an APRI) of > 2

    NOTE: Subjects in the lead-in group must not have F4 cirrhosis

    APRI formula: AST ÷ lab upper limit of normal (ULN) for AST × 100 ÷ (platelet count ÷ 100).

    NOTE: In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy or Fibroscan® is required. Liver biopsy results supersede the results obtained by Fibroscan® or Fibrosure®.
11. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements

4.3. Exclusion Criteria

1. Female subject is pregnant or breastfeeding
2. Co-infected with hepatitis B virus (HBV, positive for hepatitis B surface antigen [HBsAg]) and/or human immunodeficiency virus (HIV)
3. Abuse of alcohol and/or illicit drug use that could interfere with adherence to study requirements as judged by the investigator
4. Prior exposure to any HCV DAA
5. Requirement of any prohibited medications, as described in Section 5.8
6. Use of other investigational drugs within 30 days of dosing or plans to enroll in another clinical trial of an investigational agent while participating in the present study
7. Subject with known allergy to the study medication(s) or any of their components

8. History or signs of decompensated liver disease: ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or other clinical signs of portal hypertension or hepatic insufficiency
9. Cirrhotic and has a Child-Pugh score >6, corresponding to a Child-Pugh Class B or C. *Note: To calculate the Child-Pugh score, refer to the following website:* https://www.mdcalc.com/calc/340/child-pugh-score-cirrhosis-mortality
10. History of hepatocellular carcinoma (HCC) or findings suggestive of possible HCC
11. Active clinically significant diseases including:
    - Evidence of history of chronic hepatitis not caused by HCV, including drug-induced hepatitis, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis
    - Cardiac abnormalities/dysfunction that may interfere with subject treatment, assessment, or compliance with the protocol, including unstable angina, unstable congestive heart failure and unstable arrhythmia
    - Malignant disease or suspicion or history of malignant disease within previous 5 years (except for adequately treated basal or basosquamous cell carcinoma)
    - Any medical condition requiring chronic use of immunosuppressive drugs (e.g., for organ transplantation).
    - Subject with intestinal malabsorption (eg, structural defects, digestive failure, or enzyme deficiencies with the exception of lactose intolerance)
    - Any other clinically significant medical condition that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results
12. Clinically significant abnormal ECG at Screening, as determined by the investigator.
13. Any of the following laboratory parameters at Screening:
    - Alanine aminotransferase (ALT) or AST > 10 x ULN
    - Total bilirubin > 3 mg/dL (> 51.3 µmol/L)
    - Albumin < 2.8 g/dL (< 28 g/L)
    - International Normalized Ratio (INR) > 2.2 unless subject has a stable INR on an anticoagulant
    - Hemoglobin < 10 g/dL
    - Hemoglobin A_{1c} (HbA_{1c}) > 8.5%
    - Platelet count < 50 x 10^9/L

- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 as estimated by the Modification of Diet in Renal Disease (MDRD) formula
- Concomitant grade ≥2 toxicity of both lipase and amylase per Division of AIDS criteria (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf)

  Note: Retests of Screening laboratory parameters or assessments may be permitted once in certain scenarios with medical monitor approval. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting Screening laboratory results.

5. STUDY TREATMENTS

5.1. Description and Handling of Study Treatments

5.1.1. Test Products

The study drugs will be provided by the Sponsor. BEM (manufactured by CCI [redacted] or CCI [redacted].) will be provided as 275-mg tablets (A2--275 mg tablets). RZR (manufactured by CCI [redacted]) will be provided as 90-mg capsules.

Neither of the study drugs are authorized for marketing in any country. Justification for the doses is provided in Section 1.2.

5.1.2. Control Product(s)

No control products will be used in this study.

5.1.3. Packaging and Labeling

The Sponsor will be responsible for ensuring that study drug(s) are manufactured in accordance with applicable Good Manufacturing Practice regulations and requirements. The labels for the study drug(s) will meet applicable local regulatory requirements. Refer to the Pharmacy Manual for specific labeling information.

5.1.4. Storage and Handling

Study drugs should be stored and handled under the conditions described on the label.

5.2. Method of Assigning Subjects to Treatment

A unique subject number will be assigned to each subject at Screening. Once assigned, it will not be re-assigned to another subject. All subjects will receive the same treatment regimen of BEM and RZR for 8 weeks.

5.3. Blinding

This study is not blinded.

5.4. Dosing and Administration

5.4.1. Dispensing

Site staff will administer the first dose of study drugs at each subject's Day 1 visit. Site staff will supply each subject with enough study drug.

5.4.2. Administration Instructions

Subjects will take two (2) 275-mg tablets of BEM and two (2) 90-mg capsules of RZR once daily for 8 weeks (56 days). Study drugs will be taken together orally in the morning, at

approximately the same time each day. Study drugs can be taken with water and with or without food.

For missed dose(s), subjects will be instructed to take the missed dose(s) of study drugs as soon as possible during the same day. Subjects will be instructed not to double the next dose with a missed dose (doses should be a minimum of 6 hours apart).

In case of an incomplete dose (i.e., 1 or more tablets and/or capsules missed), the subject should take the rest of the missed tablets and/or capsules as soon as possible on the same day; they should not add the rest of the missed dose to their next dose and take more than 2 BEM tablets and 2 RZR capsules at the next dose.

Subjects will receive their first dose of study drugs in the clinic on Day 1. Thereafter subjects may self-administer the study drugs at home except for subjects who agree to additional PK and/or PK-VK sampling as part of a substudy. These subjects will be required to take their study drug in the clinic on certain days (see Section 5.4.3 and Table 3).

5.4.3. Dosing for Optional PK-only Substudy and PK-VK Substudy

Subjects participating in the optional serial PK-only substudy and/or the optional PK-VK substudy will have additional blood samples collected at certain visits. The first samples will be collected pre-dose so study staff will remind these subjects not to take study drugs on the substudy visit days until instructed to do so during the visit (see Section 6.7). The date and time of the sample collections and dosing will be recorded.

5.4.4. Treatment Compliance

Subjects will be instructed to bring back all bottles of study drugs in their original containers at every study visit through EOT. Study drug dosing by the subjects will be reconciled using pill counts at each visit by the investigator or designee to monitor adherence to the dosing regimen. In addition, subjects may be contacted by site staff or visited by home nursing between scheduled visits to ensure compliance with the dosing schedule.

5.5. Study Drug Accountability

Investigators or designees will facilitate study drug accountability by maintaining complete and accurate records of all study drugs. These include acknowledging the receipt of each shipment of study drug, maintaining subject dispensing records, and accounting for returned or destroyed study drug.

At EOS (see Section 3.1), all unused study drugs and containers will be returned to the Sponsor (or designee) or destroyed, per the instruction of the Sponsor.

5.6. Stopping Rules

5.6.1. Individual Virologic Stopping Rules

Treatment will be discontinued in any subject with on-treatment virologic failure, defined as any one of the following:

- Confirmed 1 $\log_{10}$ increase in HCV RNA from post-baseline nadir
- Confirmed increase in HCV RNA ≥ LLOQ in any subject who achieved HCV RNA < LLOQ

Confirmation should be performed as soon as possible after an initial HCV RNA value that may indicate virologic failure is reported.

After completion of study-related procedures in the current study, the investigator may offer an approved poststudy HCV treatment regimen consistent with local standard-of-care treatment guidelines to subjects who have on-treatment virologic failure or posttreatment virologic relapse. For those subjects who generally comply with the study protocol and experience lack of efficacy (failure to achieve SVR12 or SVR24) with the investigational regimen, the Sponsor may reimburse the investigator for the cost of a course of poststudy medication depending on local drug access and reimbursement policies.

5.6.2. Individual Safety Stopping Rules

Treatment will be discontinued in any subject who experiences any one of the following:

- Confirmed elevation of ALT and/or AST > 5 x baseline or post-baseline nadir, and > 5 x ULN
- Confirmed elevation of ALT and/or AST > 15 x ULN
- Confirmed elevation of ALT and/or AST > 3 x post-baseline nadir, is > 3 x ULN, and total bilirubin > 2 x ULN, without any alternative causes or reason for these elevations
- Confirmed new onset ≥ grade 3 elevation in creatinine or decreased GFR < 30 mL/min/1.73 m^2
- Any SAE or grade 4 AE (including any confirmed grade 4 laboratory abnormality reported as an AE) that are considered by the investigator to be related to study drugs, *Note: To warrant treatment discontinuation, a grade 4 laboratory abnormality should have clinical findings expected to be associated with the laboratory abnormality. Subjects with isolated asymptomatic laboratory abnormalities without any clinical correlations are allowed to remain on treatment with continued monitoring according to the preference of the investigator*.
- Pregnancy during treatment (i.e., in female study subjects)

A confirmed value is defined as one that is repeated at the next subsequent test. Any of the above laboratory results and all ≥ grade 3 new onset laboratory abnormalities must be repeated as soon as possible, preferably within 48 hours upon reporting of the initial value.

Additional follow-up and medical care, beyond what is specified in the protocol, is described in Section 5.6.3.

5.6.3. Study Stopping Rules

The study will be paused in any of the following scenarios:

- If > 3 of the first 60 subjects experience (a) confirmed elevation of ALT and/or AST > 5 x baseline or post-baseline nadir, and > 5 x ULN OR (b) confirmed elevation of ALT and/or AST > 15 x ULN OR (c) any SAE or grade 4 AE which are considered by the investigator to be related to study drugs
- If > 15 subjects at any time during the trial experience (a) confirmed elevation of ALT and/or AST > 5 x baseline or post-baseline nadir, and > 5 x ULN OR (b) confirmed elevation of ALT and/or AST > 15 x ULN
- Any SAE or grade 4 AE which is considered by the investigator to be related to study drugs
- After three or more similar grade 3 or higher AEs considered by the investigator to be related to study drugs

Any of these circumstances will result in no additional subjects being enrolled. Subjects who are tolerating treatment may continue to receive study drugs. The Sponsor will collect and review all the available data with the clinical investigators and with regulatory authorities, to obtain agreement on a plan forward.

Note: ALT/AST increases associated with virologic failure would not trigger the above stopping rules.

5.7. Premature Discontinuation

Subjects may voluntarily discontinue treatment or withdraw from the study at any time. They may also be removed from the study at the discretion of the investigator or Sponsor at any time. The investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject.

Premature treatment discontinuation may occur for any of the following reasons:

- Noncompliance with the protocol requirements
- Pregnancy
- On-treatment virologic failure, as defined in Section 5.6.1
- Adverse event precluding further study participation due to safety concerns or compliance issues
- Subject request
- Investigator request
- Sponsor request

Subjects who prematurely discontinue treatment should have an Early Termination (ET) visit and be asked to return for the scheduled post-treatment follow-up visits.

In subjects who require additional care after their participation in the trial has ended or been completed, such as that necessary to monitor an AE(s), continued follow-up and care will be

provided until resolution of the AE(s). For those who experience a lack of efficacy and virologic failure, refer to Section 5.6.1 for additional reimbursable treatment/care.

5.8. Prior Therapy, Concomitant Therapy, Permitted Therapy, Cautionary Therapy, and Prohibited Therapy

5.8.1. Prior Medication

- Subjects must be DAA-treatment-naïve, except that prior exposure to (peg)interferon with or without ribavirin is acceptable as long as it was not administered with a DAA (inclusion criterion 7, Section 4.2).
- Subjects are prohibited from use of other investigational drugs within 30 days prior to dosing in this study (exclusion criterion 6, Section 4.3)

5.8.2. Concomitant Medication

Concomitant therapy consists of any medication (eg, prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to study drug treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). Concomitant medications should be used according to their label.

5.8.3. Permitted Therapy

Subjects are also permitted to use the following therapies during the study:

- Acetaminophen (paracetamol), ibuprofen
- Anti-inflammatory drugs
- Prophylactic anticoagulation with low-dose aspirin, direct factor Xa inhibitors, or direct thrombin inhibitors
- Prescribed medications for concomitant conditions as per medical history, such as chronic supplementary oxygen, antihypertensives, antidiabetic medications, rheumatologic medications, or respiratory medications (e.g., chronic inhaled/intranasal/oral steroids)
- Hormonal contraceptives (see Section 5.9)
- Hormone replacement therapy
- Direct acting COVID medications (Paxlovid, molnupiravir, remdesivir, favipiravir, monoclonal antibodies, convalescent plasma). See Section 5.8.5 for additional details.
- Other COVID standard-of-care (SOC) therapies without direct antiviral effects (i.e., corticosteroids)

5.8.4. Cautionary Therapy

Herbal Therapies

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions (DDIs) are generally unknown.

Mitigation of Other Potential DDIs

COVID treatments with concerns for DDIs:

While remdesivir and Paxlovid are permitted, staggered dosing as specified below must be followed to minimize DDI.

Remdesivir:

As BEM and remdesivir share a common target and metabolic activation pathway, there is a potential for PK or PD drug interactions between the two, during concomitant administration of both drugs. Study drug must be dosed at least 2 hours before remdesivir.

Paxlovid:

As ritonavir is a major P-glycoprotein (P-gp) inhibitor (see below), subjects enrolled in the study who are taking Paxlovid should not take Paxlovid until at least 2 hours after taking BEM/RZR. See below for additional P-glycoprotein – based DDIs

For more details regarding potential DDIs, refer to the BEM and RZR Investigator's Brochures.

P-glycoprotein-Based Inhibition

Concomitant use of P-gp inhibitors is permitted but must be taken at least 2 hours after administration of study drug. Common examples of P-gp inhibitors include cyclosporine, carvedilol, imidazoles, macrolides, ritonavir, and verapamil.

For a full list of P-gp inhibitors, refer to: https://go.drugbank.com/categories/DBCAT002667

Subjects taking digoxin must do so at least 2 hours after taking study drug.

Gastrointestinal Acid Reduction-Based Interaction

Gastrointestinal acid reducing agents such as proton-pump inhibitors, H2 blockers and antacids may reduce the solubility of BEM. Subjects taking these agents will do so at least 2 hours after taking study drug.

Permitted concomitant medications should be administered only as medically necessary during the study. Any use of concomitant medications should be recorded and entered into the case report form.

For more details regarding the effects of co-administered therapies on RZR and BEM, refer to the respective Investigator's Brochures.

5.8.5. Prohibited Therapy

Concomitant use of the following is prohibited:

- Investigational drugs (other than protocol-mandated study treatment)
- HCV treatments (other than protocol-mandated study treatment)
- Hydroxychloroquine or amiodarone

- Strong and moderate inducers of cytochrome P450 3A and/or P-gp including anti-infectives (nafcillin, rifampin), anticonvulsants (carbamazepine, phenytoin, phenobarbital), endothelin antagonists (bosentan), and wakefulness-promoting agents (modafinil). For a comprehensive list of cytochrome P450 3A inducers, refer to: https://go.drugbank.com/categories/DBCAT000492; for a comprehensive list of P-gp inducers, refer to: https://go.drugbank.com/categories/DBCAT002666

5.9. Contraception Requirements

A female is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Females of childbearing potential must be established on their chosen method of contraception at screening.

Female subjects of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use one of the following methods of acceptable effective contraception [8] during the treatment period and for 30 days after the final dose of study drugs:

- Bilateral tubal ligation
- Male sterilization
- Hormonal contraceptives
- Intrauterine devices (whether or not they are hormone-releasing)
- Male or female condom with or without spermicide (male and female condom cannot be used together)
- Sexual abstinence

  Note: The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form (ICF).

- Cap, diaphragm, or sponge with spermicide.

Should acceptable effective methods of contraception be more restrictive than the methods listed above per local regulations, guidance, or investigator practice, a more restrictive list may be included within the site/country-specific Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF.

6. STUDY PROCEDURES AND GUIDELINES

Study-specific assessments are summarized in Table 2. An "X" indicates when the assessments are to be performed. The screening window is 28 days but may be extended to 42 days for extenuating circumstances with Sponsor approval. Such circumstances may include awaiting reporting of laboratory results or scheduling assessment of cirrhosis (e.g., FibroScan®) if needed.

When feasible, visits may be conducted remotely (e.g., via telephone or telemedicine), in clinic, or at home.

Table 2: Schedule of Assessments

			Treatment Period						Follow-up Period		
	Screening[a]	Baseline	± 1 day		± 3 days		+ 3 days		Following Last Treatment Visit; ± 5 days		
Study Week/Day:	**Day -28 to Day -1**	**Day 1[b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57[c]**	**ET**	**Week 4**	**Week 12**	**Week 24**
Eligibility											
Informed consent	X										
Medical history	X										
Demographics	X										
Inclusion/Exclusion Criteria	X	X									
Physical Examination and Vital Signs											
Complete physical examination	X	X					X	X			
Symptom-targeted examination			X	X	X	X			X		
Vital signs	X	X	X	X	X	X	X	X	X		
Height (screen only) and weight	X	X			X		X	X			
Triplicate 12-lead ECG[d]	X	X			X		X	X	X		
Liver staging	X										
Laboratory											
Clinical labs and urinalysis	X	X	X	X	X	X	X	X	X		
HBV (HBsAg), HCV (anti-HCV Ab), and HIV screen; hemoglobin A_{1c}	X										
Pregnancy test[e]	X	X			X	X	X	X	X		
Pharmacodynamics and Pharmacokinetics											
HCV genotyping	X										
HCV RNA quantitation	X	X	X	X	X	X	X	X	X	X	X
Viral resistance sample[f]	X	X	X	X	X	X	X	X	X	X	X

	Screening[a]	Baseline	Treatment Period						Follow-up Period		
			± 1 day		± 3 days		+ 3 days		Following Last Treatment Visit; ± 5 days		
Study Week/Day:	**Day -28 to Day -1**	**Day 1[b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57[c]**	**ET**	**Week 4**	**Week 12**	**Week 24**
PK Sample[g]		X	X	X	X	X	X	X			
Optional PK-only substudy[h]				Serial blood sampling at any treatment period visit as early as Week 2							
Optional PK/VK substudy[h]		Days 1, 2, and 3									
Study Intervention											
Study drug administration		X	At-home dosing for full treatment period (Days 1-56) unless otherwise specified								
Review compliance with study drugs[i]			X	X	X	X	X	X			
Adverse Event and Concomitant Medication Monitoring											
Concomitant medications[i]	X	X	X	X	X	X	X	X	X		
AEs[i]	X	X	X	X	X	X	X	X	X		
SAEs[i]	X	X	X	X	X	X	X	X	X	X	X

AEs = adverse events; anti-HCV Ab = anti-HCV antibody; APRI = aspartate aminotransferase (AST) to platelet ratio index; BMI = body mass index; ECG(s) = electrocardiogram(s); ET = early termination; HBsAg = Hepatitis B virus surface antigen; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human Immunodeficiency virus; PK = pharmacokinetic; SAEs = serious adverse events; VK = viral kinetics

[a] Screening window may be extended to 42 days for extenuating circumstances with Sponsor approval.

[b] Day 1 assessments performed prior to dosing.

[c] The last dose is on Day 56. The last visit of the treatment period shall occur no sooner than Day 57 and no later than Day 60 (inclusive).

[d] Three consecutive determinations collected, with no less than 1 minute between individual ECGs. Complete ECGs prior to any blood draws.

[e] For females of childbearing potential, serum or urine is acceptable.

[f] Plasma samples collected for resistance testing. At least one baseline resistance sample is needed (Screening and/or Day 1 predose); there is no protocol deviation if there is one evaluable baseline sample for resistance testing. In addition, the resistance sample is not required for screening and eligibility purposes.

[g] On Day 1, the PK sample will be obtained predose. The sampling time and time of last dose must be recorded.

[h] See Table 3

[i] Subjects may be contacted between visits to assess compliance, concomitant medications, and AEs/SAEs.

Table 3: Optional PK-only and PK-VK Substudies: Sampling Schedule

Visit	Serial PK-Only Substudy Sampling Time	Serial PK/VK Substudy Sampling Time
Day 1	Not applicable [a]	PK Sample [a]: 0.5 (± 15 minutes), 1 (± 15 minutes), 2, 3, 4, 6, 8 hours postdose[b] VK Sample [a]: 0.5 (± 15 minutes), 1 (± 15 minutes), 2, 3, 4, 6, 8 hours postdose[b]
Day 2	Not applicable	PK Sample: Pre-dose (~24 hours post Day 1 dose) [c] VK Sample: Pre-dose (~24 hours post Day 1 dose) [c]
Day 3	Not applicable	PK Sample: Pre-dose (~48 hours post Day 1 dose) [c] VK Sample: Pre-dose (~48 hours post Day 1 dose) [c]
Any planned Treatment-Period Visit, as early as Week 2 [a]	0.5 (± 15 minutes), 1 (± 15 minutes), 2, 3, 4, 6, and 8 hours postdose[b]	Not applicable

[a] No additional predose samples are needed on Day 1 for either substudy nor at the Week 2 (or later) visit for the PK-only substudy; the results of the pre-dose PK and viral load samples that will be collected as part of the main study visit schedule will also be used as pre-dose values for the substudy analyses.
[b] ± 30-minute sampling window for postdose samples, unless otherwise specified.
[c] ± 2-hour sampling window
PK = pharmacokinetic; VK=viral kinetics

6.1. Medical History and Demographics

± 2-hour sampling window

Complete medical history will be obtained at Screening. Information about HCV disease history will be collected, including prior treatments (if treatment-experienced), response to prior treatment and prior assessment(s) of cirrhosis (if available). Subjects will also be questioned about alcohol and drug use.

Demographic data (age, gender, ethnicity/race, body weight, height, Body Mass Index [BMI]) will be recorded.

6.2. Physical Examination and Body Weight

A complete physical examination will be performed by a medically qualified individual at specified visits. 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.

At visits not requiring a complete physical examination, a symptom-targeted physical exam will be done if medically indicated.

Body weight will be recorded, and BMI will be calculated at specified visits (height is to be recorded at screening).

6.3. Vital Signs

Vital sign measurements (body temperature, pulse rate and blood pressure) will be measured at each specified visit after subjects have had at least 3 minutes of rest. Vital signs can also be monitored during the study when judged necessary by the investigator or designee.

6.4. 12-Lead Electrocardiogram

Triplicate ECGs will be collected after subjects are supine for 5 minutes. Each reading will be performed no less than 1 minute apart from each other. The mean QTcF value from the three readings will be used to include subjects in the study (per the inclusion criterion) and mean values of the triplicate readings will be used for analysis.

For visits in which ECGs and blood draws are both performed, ECGs will be conducted prior to the blood draw since the blood draw can impact the ECG reading.

6.5. Liver Staging

Liver staging is to be determined at Screening as specified in inclusion criterion 10 (Section 4.2).

6.6. Laboratory Evaluations

Clinical laboratory evaluations will be performed at specified visits. The following tests will be conducted only at Screening:

- Serologies for HCV (anti-HCV antibody), HBV (HBsAg), and HIV
- HbA_{1c}

The following hematology, serum chemistry, coagulation, and urinalysis evaluations will be conducted at specified visits. The investigator or designee will assess each abnormal value to determine if it is clinically significant.

- 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

Laboratory samples will be sent to a central laboratory for analysis. However, for an individual visit(s), a second set of samples may be drawn by the investigator and sent to the site's local

laboratory to obtain "STAT" results, if needed for safety assessment, this includes Screening assessments.

The total volume of blood withdrawn during the course of the study should not exceed 500 mL per subject over any two-month period. However, it is possible that the total blood donation may be higher if repeat blood samples are required for safety assessments.

6.7. Pharmacodynamics and Pharmacokinetics

6.7.1. Hepatitis C Virus Genotyping, RNA Levels, and Mutation Analysis

- HCV genotyping will be performed at Screening
- HCV RNA levels will be determined at Screening, Baseline and at each subsequent visit

  Note: HCV genotyping and HCV RNA quantitation will be performed using a validated commercial assay.
- Samples will be collected at each visit to assess resistance.

Additional samples for assessing HCV RNA levels will be obtained in an optional PK-VK substudy, which is described in Section 6.7.3.

6.7.2. Pharmacokinetic Sampling for All Subjects

For all subjects, a single blood sample for PK analysis will be collected at Baseline (before the first dose; Table 2); the sampling time will be recorded. During the other planned treatment period visits, a single blood sample for PK analysis will be obtained before the subject is released from the clinic; the date and time of the last dose of study drugs and of the PK sample will be recorded.

Additional samples for PK analyses will be obtained as part of the optional PK-only substudy described in Section 6.7.3.

6.7.3. Optional Substudies

At clinical sites that agree to participate, optional PK-only and PK-VK substudies will be conducted on approximately 100 subjects who provide consent to participate in either or both substudies (Table 3). In addition to the samples normally collected at scheduled visits, these subjects will provide additional samples as shown in Table 3. Subjects participating in either or both of these studies should take their study drug in the clinic on sampling days after the predose samples are collected.

Date and time will be recorded for the following:

- last dose of study drug
- each PK and/or VK sample collection
- dosing

Blood samples will be collected by direct venipuncture. However, as an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the forearm vein of the subject.

6.7.4. Sample Processing, Storage, and Shipping

All samples will be processed, split (as applicable), stored, and shipped according to the sample processing instructions supplied by the central laboratory.

Blood samples may be stored for up to 10 years under the control of the Sponsor. Samples may be used by the Sponsor, Sponsor partner, or by other companies belonging to or collaborating with the Sponsor only for the testing specified in this protocol.

6.7.5. Bioanalytical Methods for Pharmacokinetic Samples

Plasma concentrations of the study drugs and their metabolites (as appropriate) will be measured according to validated bioanalytical methods. Samples from all subjects who received at least one dose of both study drugs will be analyzed.

7. ADVERSE EVENTS

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product(s) and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product(s), whether or not considered related to this medicinal product(s). The worsening of a pre-existing condition (i.e., clinically significant change in frequency and/or intensity) that occurs during study participation is also an AE.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug(s) caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug(s) and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug(s).

An AE may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication(s); it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the qualified investigator or medically qualified designate considers to be clinically significant

Symptoms or conditions reported prior to consent are not AEs; these will be recorded as part of medical history.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs/, or worsens during the study period. Planned (elective) surgical measures and the conditions(s) leading to these measures are not AEs, if the condition(s) existed or was (were) known before the time of informed consent. In the latter case, the condition should be reported as medical history.

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect

- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the qualified investigator)

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if they meet the definition above. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described above. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin). Laboratory abnormalities that do not require medical intervention or action are generally not considered AEs.

Laboratory abnormalities will be graded based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 [9]. If a value falls within the local laboratory normal range, then it will not be graded. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.1.1. Severity Assessment

The investigator or the designated person will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's eCRF. In classification of AEs, the term "severe" is not the same as "serious." Severity is a description of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning and meets one or more of the SAE criteria described above.

The DAIDS criteria [9] will also be used for assessing AEs. All AEs will be graded as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life-threatening), or grade 5 (death) according to the DAIDS criteria. Every effort will be made to obtain an adequate evaluation of the severity.

7.1.2. Causality Assessment

The qualified investigator or a medically qualified designate will determine the relationship of any AE to study drugs using the following guidelines in Table 4.

Table 4: Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	There is evidence to suggest a causal relationship between the drug(s) and the adverse event (eg, the adverse event is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure).
No Reasonable Possibility	There is no evidence to suggest a causal relationship between the drug(s) and the adverse event.

7.2. Routine Reporting

For the purposes of this study, all AEs (serious and non-serious) will be recorded in the eCRF from the time of informed consent until 4 weeks after the last dose of study drugs. All SAEs will be recorded from the time of informed consent until the end of the study.

During these periods, all AEs spontaneously reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded and reported in the eCRF.

Any AE which remains unresolved as of the last visit will require follow-up until the AE has been resolved, a reasonable explanation for its persistence found, or is deemed chronic or stable by the investigator. It is the investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification of AEs will be performed by System Organ Class and Preferred Term using The Medical Dictionary for Regulatory Activities (MedDRA).

Electronic case report form procedures for AE and SAE reporting can be found in the eCRF completion guidelines. Paper SAE forms are to be used only if the Electronic Data Capture (EDC) system is unavailable.

7.3. Serious Adverse Event Reporting

Clinical sites must notify the Sponsor and its designee CCI [redacted] of any SAE, without regard to causality, within 24 hours after becoming aware of its occurrence. Any non-serious AE which worsens and eventually meets the criteria for an SAE must also be reported as a new SAE.

Information regarding SAEs will be transmitted using the Serious Adverse Event Form in the EDC system; this form must be completed by a member of the investigational site staff within 24 hours of awareness. The form should include a clearly written narrative describing signs, symptoms and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be reported as soon as it is available.

In the event EDC entry is not possible (e.g., system failure or access problems at the site), the site should complete the paper Serious Adverse Event Form and provide it within 24 hours of awareness to the contacts listed below:

Email (primary): PPD

Fax (back-up): PPD

Email (back-up): PPD

Contact information for the Sponsor's physician is also listed below, should the sites need to contact the Sponsor to discuss any medical, safety-related questions or SAEs:

PPD

If PPD is not reached by telephone call, and does not confirm receipt of a notifying text or email, the following Atea Clinical contact should be notified:

PPD

An unlisted (unexpected) AE is one in which the nature or severity is not consistent with the applicable product reference safety information. For investigational product(s), the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure(s). At this time in the clinical development of BEM, there are no clinical AEs or clinically significant laboratory abnormalities that are considered to be "expected" with BEM, at any dose level. Investigators will be notified, and the Investigator Brochure will be updated, if any pattern of tolerable AEs or laboratory abnormalities is found to be related to BEM dosing during studies going forward.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves;
- the event stabilizes;
- the event returns to baseline if a baseline value is available;
- the event can be attributed to agents other than the study drugs or to factors unrelated to study conduct;

- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any SAE reports will be reported by the investigators (or designee) to their local IRB/IEC in accordance with local reporting requirements and reporting timelines.

Similarly, the Sponsor (or designee) will determine whether an SAE must be reported in an expedited manner to regulatory authorities, in accordance with local requirements. If so, the Sponsor (or designee) will report the event to the local regulatory authorities (eg, EudraVigilance Clinical Trials Module) in accordance with applicable reporting timelines. Aggregate and periodic reporting (e.g., annual report, DSUR, etc.) to regulatory authorities will be satisfied based on local requirements.

7.4. Pregnancy Reporting

From Day 1 through the last follow-up visit (or until 30 days after the last dose of study drug for subjects who prematurely discontinue and do not enter the follow-up period), all initial reports of pregnancy in female subjects must be reported to the Sponsor (or designee) using the contact information described in Section 7.3.

Within 24 hours of their knowledge of the event, investigational staff must complete and submit the Pregnancy Notification Form . Pregnancies will be followed up to determine the outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies or maternal and/or newborn complications. After the expected pregnancy end date, the Sponsor or designee will provide the site with the designated Pregnancy Outcome Form for completion and reporting to the CCI [redacted] Abnormal pregnancy outcomes are considered SAEs and must be reported using the designated Serious Adverse Event Form.

Any female study subject who becomes pregnant during treatment must immediately discontinue study drugs.

Pregnancy reporting will be in accordance with local requirements, and may be adapted per country as required by regulations.

8. STATISTICAL ANALYSES

The following sections briefly summarize the statistical analysis. A statistical analysis plan (SAP) describing the detailed methodology will be prepared prior to database lock.

Results of all efficacy analyses will be presented by genotype and cirrhotic status.

Interim and final analyses will be reported/posted in accordance with local/regional requirements.

8.1. Analysis Populations

8.1.1. Screened Patients

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

8.1.2. Safety Population

The safety population will include all subjects who received at least one dose of either study drug.

8.1.3. Per Protocol Population

The PP population will consist of all subjects who:

- Meet all inclusion/exclusion criteria
- Do 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)
- Have a collected or imputed posttreatment viral load assessment at posttreatment Week 12 (posttreatment Week 4 for lead-in subjects) unless the subject discontinues early for virologic failure or AE, in which case the ET visit may be used
- Complete treatment (being in ≥90% compliance with the study drug regimen), discontinue treatment early due to virological failure or discontinue treatment early due to a drug-related AE

  Note: 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.

This population will be used for all efficacy analyses.

8.1.4. PK Compliant Per-Protocol (PK-PP) Population

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

- Meet all inclusion/exclusion criteria.
- Do 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).

- Have a collected or imputed posttreatment viral load assessment at posttreatment Week 12 (posttreatment 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.
- Complete treatment, discontinue treatment early due to virological failure, or discontinue treatment early due to a drug-related AE.
  - Completing treatment is defined as being in ≥90% compliance with the study drug regimen (as calculated using drug compliance data collected on the eCRF), and
  - Adequate exposure will be 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.

8.1.5. 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.

8.2. Endpoints

8.2.1. Primary Endpoint

The primary efficacy endpoint is SVR12.

8.2.2. Secondary Endpoints

Secondary efficacy endpoints include:

- Virologic failure
- SVR24.

8.2.3. 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

8.2.4. Safety Endpoints

Safety endpoints are the incidence of AEs, SAEs and, AEs resulting in treatment discontinuation; clinical laboratory abnormalities; vital sign measurements; and ECG parameters.

8.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, sex [male/female], race [American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islanders; White; Other], region, BMI, weight) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group. Demographics and baseline characteristics will be listed by subject. Other data to be listed by subject will include urinary drug screen, serology results, medical history, baseline physical examination findings, and prior and concomitant medications.

8.4. Efficacy Analyses

8.4.1. Primary Analyses

In this analysis, results are pooled across genotypes and cirrhosis status as it is expected that efficacy will be consistent across these groups. To evaluate the robustness of results, additional analyses, including summarization by genotype and cirrhosis status, will be carried out.

The proportions of subjects in the PP population(s) achieving SVR12 will be estimated and presented with associated two-sided 95% confidence intervals (CIs), which will be constructed using the Wilson score method. Reasons for failure to achieve SVR12 will be summarized.

8.4.2. Secondary Analyses

Secondary analyses will include:

- The proportion of subjects in the PP population(s) experiencing virologic failure (on treatment or post-treatment relapse) by 12 weeks post treatment), estimated and presented with 95% CIs.
- The proportion of subjects in the PP population(s) achieving SVR24, analyzed using the same method as for SVR12.

Additional exploratory analyses will be performed and may include (but not be limited to) the following:

- The proportion of subjects in the PP population(s) achieving SVR12 by baseline NS5A and NS5B RAVs (yes/no), estimated and presented with 95% CIs.
- Emergence of NS5A and NS5B RAVs in the PP population(s), tabulated with proportions and CIs in subjects who experience virologic failure
- Assessment of response (e.g., SVR12 rates) by demographics and/or baseline characteristics including prior HCV treatment, baseline viral load, etc.

- HCV RNA change from baseline over time
- Exposure-response relationships

Additional details will be provided in the SAP.

8.5. Safety Analyses

Study treatment exposure (such as treatment duration and total dose received) will be summarized with descriptive statistics.

Treatment-emergent AEs and graded laboratory abnormalities, defined as any new or worsening AE/laboratory parameter beginning on or after the first dose of study drugs through 4 weeks after the last dose, will be included in the analysis.

Incidence and frequency of subjects experiencing AEs, SAEs, AEs resulting in treatment discontinuation, and AEs resulting in study discontinuation will also be summarized. Adverse events will be coded using MedDRA. The incidence and frequency of subjects with treatment-emergent adverse events will be tabulated by primary SOC and PT. The tabulation of the number of subjects with treatment-emergent AEs will also be provided by grade and relationship to study drug.

Changes from baseline in laboratory tests and vital signs will be summarized. Laboratory abnormalities will be graded in accordance with the DAIDS severity scale[9] where applicable. Shift tables for treatment-emergent laboratory abnormalities will be presented.

8.6. Pharmacokinetic Analyses

Plasma concentrations of the study drugs and metabolites over time will be listed by time point and summarized using descriptive statistics, as applicable.

Derived PK parameters (e.g., C_{max} and AUC) will be summarized descriptively for subjects participating in the optional substudy.

Additional details will be provided in the SAP.

8.7. Interim Analyses

An interim analysis will be performed on data from the lead-in group using the PP population(s). The proportion of subjects achieving SVR4, defined as HCV RNA < LLOQ at 4 weeks posttreatment, will be presented with 2-sided 95% 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% that is not due to poor compliance (> CCI 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 (Section 5.6.3).

8.8. Sample Size

The primary analysis will be based on the PP population. The Sponsor expects approximately 95% of the enrolled subjects to meet the PP criteria. Therefore, the PP population is expected to be 71 subjects with GT3 infection, and 266 subjects across all genotypes based on target enrollments provided in Table 1.

Table 5 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 5: 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

9. ETHICS

9.1. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

This protocol and the ICF will be submitted to an IRB or IEC prior to initiation of the study and the study will not start until the IRB or IEC, as applicable, has approved the documents.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles in the latest version of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline E6 (R2) for Good Clinical Practices (GCP) and local regulations.

9.3. Participant Information and Consent

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out, and the potential hazards. Once this essential information is provided to the subject, the subjects will be required to read, sign and date a written informed consent form prior to enrollment. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their ICF.

If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

Subjects will also be consented for participation in the optional PK-only substudy and/or the optional PK-VK substudy. Separate consent is required for participation in each substudy.

9.4. Subject Confidentiality and Personal Data Protection

The investigators and the Sponsor (and organizations processing data on its behalf [Processors]) will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects will be identified by a unique subject identifier on all study documents provided to the Sponsor (and Processors). In compliance with local regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and IRB/IEC access to review the subject's original medical records for verification of study-related procedures and data.

Supplemental Information for Participating Sites Located in the European Union (EU)

The collection of data from European patients in the study constitutes a processing of personal data within the meaning of Article 4 of the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (GDPR).

At an organizational level, to meet European requirements the Sponsor has appointed a certified Data Protection Officer (DPO) in charge of ensuring compliance with data protection regulations. The DPO oversees the conduct of the required Data Protection Impact Assessment (DPIA) to assess and protect rights and freedoms of data subjects regarding processing

operations. All Processors are bound by a data protection agreement (DPA). If personal data are transferred to a third country within the meaning of the General Data Protection Regulation (GDPR), the DPA contains the Standard Contractual Clauses established by the European Commission. The DPO is also in charge of any data subject request and can be contacted directly by the data subject through the email provided in the patient information sheet.

The subjects and healthcare professionals involved in this study will be informed on the type of data collected and processed about them, for which objective and on which legal basis; they will also be informed about their rights on their personal data, and how to exercise their rights.

At a technical level, the Sponsor has implemented and maintains, and requires that Processors have implemented and maintain, measures such that personal data are stored in a secured environment, encrypted, and partitioned from other data. Access to personal data is limited to relevant staff through access policies. All persons accessing data are bound by a confidential clause or professional secrecy.

Subjects will be assigned a unique identifier (data pseudonymization) and will not be identified by name in eCRFs, study databases, study-related forms, study reports, or any related publications. The key to identify subjects is stored in a secure manner by each study site.

The Sponsor will regularly review its technical and organizational security measures and update them to take into account any evolution on technological developments. The Sponsor may apply additional specific statutory requirements, where applicable in the national laws.

Besides technical and organizational measures, the Sponsor, by means of internal measures and imposed contractual clauses to Processors, further maintains the confidentiality of records and personal data of subjects.

The Sponsor has put in place a functional process of reporting of any data breach occurring at the Sponsor's or Processor's facilities and premises which involve personal data of subjects in the clinical study. In case of the occurrence of any data breach, the Sponsor, in consultation with its DPO, will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, subjects will be informed by the Sponsor (via clinical study site).

10. DATA COLLECTION, RETENTION, AND MONITORING

10.1. Case Report Forms

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. Representatives of the Sponsor, the CRO, or their designee(s) will train designated site staff 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 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 eCRFs will be retained by the investigator. Copies of the eCRFs will be provided to the Sponsor (or designee).

10.2. Data Management and Processing

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.

10.3. Quality Assurance

This study will be conducted in accordance with standard operating procedures of the CRO(s) that will conduct the study. These standard operating procedures are designed to ensure adherence to ICH Guideline E6 (R2) for GCP.

All vendors and clinical sites will be subject to inspection by the Sponsor (or designee) to ensure that the data are generated, documented, and reported in compliance with the study plan and applicable local regulatory requirements.

10.4. Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product or at least 25 years after the end of the trial, whichever is longer. However, these documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

10.5. Monitoring of the Study

In the event of any local disease outbreak or global pandemic (eg, COVID-19), any training or monitoring described in this section may be conducted remotely or via telephone or video. Depending on the situation over time at each site, it is possible that trainers or monitors may be on-site.

Before study initiation, representatives of the Sponsor or its designee(s) will review the protocol and eCRF with the investigators and their staff and perform study-specific training.

During the study, the study monitor and CRO will check documentation, either remotely or on-site, to ensure completeness of records, accuracy of entries on the eCRFs, adherence to the protocol and to GCP, progress of enrollment, and confirmation study drug supply/logistics. Key study personnel must be available to assist the study monitor during remote or on-site visits.

The investigator must maintain source documents for each subject in the study, which may consist of case and visit notes (hospital or clinic medical records). All information on eCRFs must be traceable to these source documents in the subject's file. For any on-site visits, the investigator must give the study monitor access to any relevant source documents to confirm their consistency with the eCRF entries. The investigator must also keep records documenting the informed consent process. Information in source documents that could identify the subjects (such as the subjects' names) will not be forwarded to the Sponsor (or its designee(s)).

Depending on COVID-19 restrictions, the Sponsor or its representative(s) may visit the study facilities in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will then permit any trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11. ADMINISTRATIVE PROCEDURES

11.1. Adherence to Protocol

Excluding an emergency in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and local regulatory guidelines.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB/IEC for approval.

11.2. Investigator Responsibilities and Delegation of Investigator Duties

The investigator will ensure that all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator will maintain a list of subinvestigators and other appropriately qualified persons to whom he/she delegates significant trial-related duties.

11.3. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the investigator (or designee) should promptly inform the trial subjects, should assure appropriate follow-up for the subjects and should inform the regulatory authority(ies)/IRB/IEC, when required.

11.4. Publications

This is a multicenter clinical trial sponsored by Atea Pharmaceuticals. Any formal presentation or publication of data collected for this study will be considered as a joint presentation or publication by the clinical investigator(s) and the Sponsor. As is customary for multicenter trials, publication or presentation of data from individual study centers will not be allowed prior to the publication of the principal study abstract(s) and manuscript(s), without the explicit written permission of Atea Pharmaceuticals. Subsequent publications or presentations of data from the study must receive review and approval from Atea Pharmaceuticals before submission.

Any publication of data generated from this study will adhere to the guidelines delineated in the Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3 [10]. In addition, Atea Pharmaceuticals will determine authorship of the principal study manuscript(s) in accordance with guidance provided by the 2022 International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals[11]. The publication or presentation of any study results shall comply with all applicable privacy laws.

12. REFERENCES

1. World Health Organization (WHO). Hepatitis C Fact Sheet. Available at http://www.who.int/news-room/fact-sheets/detail/hepatitis-c. 2022.Accessed 18 May 2022.
2. Viral Hepatitis C Surveillance Report 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepC.htm
3. EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Gilead Sciences, Inc. Foster City, CA. August 2017.
4. HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. US Prescribing Information. Gilead Sciences, Inc. Foster City, CA. April 2017.
5. MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use. US Prescribing Information. AbbVie, Inc. North Chicago, IL. August 2018.
6. European Medicines Agency. Committee for Medicinal Products for Human Use. Guidelines on the evaluation of direct acting antivirals for the treatment of chronic hepatitis. 23 June 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-evaluation-direct-acting-antivirals-treatment-chronic-hepatitis-revision-1_en.pdf. Accessed 22 Nov 2022.
7. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015 Sep;62(3):932-954. doi: 10.1002/hep.27950.
8. Head of Medicines Agency: Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. Version Date 09 Sept 2020. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf
9. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf
10. Battisti WP, Wager E, Baltzer L, et al. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163(6):461-464. https://doi.org/10.7326/M15-0288
11. Uniform Requirements for Manuscripts. https://www.icmje.org/icmje-recommendations.pdf

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Approval Task Task Verdict: Approved	[redacted]

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