Official Protocol Title:	A Phase 2, Open-Label Clinical Trial to Study the Efficacy and Safety of 12 weeks of the Combination Regimen of MK-3682 + Ruzasvir in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5 or 6 Infection
NCT number:	NCT02956629
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TITLE:

A Phase 2, Open-Label Clinical Trial to Study the Efficacy and Safety of 12 weeks of the Combination Regimen of MK-3682 + Ruzasvir in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5 or 6 Infection

IND NUMBER: 123,749
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 6.0 7.1.5.6 7.1.5.7 8.6.3 12.3	Trial Summary Trial Design Trial Flow Chart Discontinued Subjects Continuing to be Monitored in the Trial Evaluation of Laboratory Safety Signals Summaries of Baseline Characteristics, Demographics, and Other Analyses Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	The 3-year long-term follow-up period has been removed from the trial.	These changes were made to remove the 3-year long-term follow-up period of the trial. Merck has made a strategic decision to discontinue the development of the investigational combination regimens MK-3682C (ruzasvir/uprifosbuvir) and MK-3682B (grazoprevir/ruzasvir/ uprifosbuvir). As a result, there is no need to obtain long-term follow-up on the persistence of resistance substitutions to ruzasvir or uprifosbuvir. The 3-year long-term follow-up period was observational; therefore, the removal of the 3-year long-term follow-up will have no impact on the safety of the study participants.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3682 + ruzasvir (RZR) for 12 weeks in Subjects with HCV GT1-6 Infection
Sponsor Product Identifiers	MK-3682 + RZR
Trial Phase	Phase 2
Clinical Indication	Treatment of hepatitis C virus (HCV) infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Chronic HCV genotype (GT) 1-6 infected, treatment-naïve and interferon-based treatment-experienced, with or without HIV infection, cirrhotic and non-cirrhotic subjects will be assigned to receive MK-3682 (450 mg) + RZR (180 mg) (MK-3682 + RZR) for 12 weeks. Approximately 250 subjects will be allocated to receive MK-3682 + RZR for 12 weeks. The first 50 subjects will be allocated to treatment regardless of GT. If the general safety and tolerability of these first 50 subjects is assessed to be acceptable after TW4, then the remaining targeted allocation of 200 subjects will be based on GT (GT1, GT2, GT3, GT4, GT5, or GT6). The first 50 subjects will be included in the overall allocation target of the trial as shown below. MK-3682 + RZR for 12 weeks (n=250): • GT1 (n=50) • GT2 (n=50) • GT3 (n=50) • GT4 (n=50) • GT5 (n=25) • GT6 (n=25) Note that the treatment regimen with MK-3682 + RZR for subjects with a particular GT will be extended to 16 weeks' duration and ribavirin (RBV) will be added, if the efficacy criteria for stopping enrollment/treatment allocation are met for that particular GT.
Number of trial subjects	Approximately 250 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 46 weeks from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 42 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 45 days, each subject will receive assigned treatment for approximately 12 weeks. After the end of treatment, each subject will be followed for 24 weeks. For subjects who may have their treatment regimen modified to MK-3682 + RZR for 16 weeks + RBV, trial participation will be approximately 46 weeks.
Randomization Ratio	Not Applicable

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multi-site, open-label trial to evaluate a novel 2-drug combination regimen (MK-3682 450 mg and MK-8408 [hereafter referred to as ruzasvir (RZR)] 180 mg) in subjects with chronic hepatitis C virus (HCV) to be conducted in conformance with Good Clinical Practices (GCP). Subjects with genotype (GT) GT1, GT2, GT3, GT4, GT5, or GT6 infection will be enrolled. Subjects may be treatment-naïve (TN) or treatment-experienced (TE) with a prior interferon (IFN)-based therapy, but subjects may not have previously received treatment with HCV direct-acting antiviral (DAA) therapy. Subjects may be cirrhotic or non-cirrhotic, and mono-infected with HCV or co-infected with human immunodeficiency virus (HIV). Enrollment will be monitored in real-time, with a target allocation of approximately 25% to 30% cirrhotic subjects for each GT for GT 1-4. As the prevalence of GT5 and GT6 is lower, enrollment of these subjects may be limited. Enrollment of subjects with GT5 and GT6 is approximate with the assumption that full enrollment of these GTs may not be reached, and the proportion of cirrhotic subjects allocated for each of these GT5 and GT6 is not stipulated.

A total of approximately 250 subjects will be allocated to receive 12 weeks of treatment with MK-3682 (450 mg) + RZR (180 mg) (termed MK-3682 + RZR) with target allocation based on GT (GT1, GT2, GT3, GT4, GT5, or GT6) see Table 1.

- The first 50 subjects will be allocated to treatment regardless of GT or fibrosis stage.
- After the first 50 subjects (of any GT) are allocated to treatment, additional allocation will pause to assess general safety and tolerability. This will be assessed after these first 50 subjects complete TW4, as this allows for steady state of drug to be achieved for ≥2 weeks. As detailed in Section 5.11.1, this pause in treatment allocation will allow for assessment of any drug-related safety events.
- These first 50 subjects will be included in the overall treatment allocation target of the trial, and counted towards the GT and fibrosis stage allocation targets shown in Table 1.
- If general safety and tolerability is assessed to be acceptable, the remaining 200 subjects will be allocated to treatment with an overall target allocation based on GT (GT1, GT2, GT3, GT4, GT5, or GT6), see Table 1.

For subjects who remain on treatment, the treatment regimen with MK-3682 + RZR for subjects with a particular GT will be extended to 16 weeks' duration and ribavirin (RBV) will be added, if the efficacy criteria for stopping enrollment/treatment allocation are met for that particular GT (see Section 5.11.4). For example, if efficacy criteria for stopping enrollment/treatment allocation are met for GT1-infected subjects at TW8, GT1-infected subjects already on treatment will receive MK-3682 + RZR for an additional 8 weeks (i.e., 16 weeks' total duration) + RBV for 8 weeks.

All subjects will be followed for 24 weeks after the end of treatment. Safety and tolerability will be carefully monitored throughout the study by the Sponsor in accordance with standard procedures.

Pharmacokinetic (PK) and Intensive Pharmacodynamic (PK/PD) Sub-studies

The purpose of the PK sub-study is to evaluate concentrations of MK-3682 and its metabolites, and RZR, as well as the PK-efficacy and PK-safety relationships. The purpose of the intensive PK/PD sub-study is to evaluate whether early viral kinetics can aid in developing a PK/PD model that can predict combinations that may be efficacious with various treatment durations.

Pharmacokinetics will be assessed in all subjects (including the first 50 and the subsequent 200), as specified in Section 4.2.5.3.

The intensive PK/PD group will only be offered to subjects once treatment allocation is opened to the subsequent 200 subjects (and will exclude the first 50 subjects). A subset of the remaining 200 subjects will participate in an intensive PK/PD group to include additional assessments for PK/PD. A total of approximately 30 subjects, (5 subjects of each GT1-6, regardless of fibrosis stage) who consent to participate, will undergo additional PD evaluations as specified in Section 4.2.5.4, and these subjects will also have additional electrocardiographs (ECGs) performed as specified in Section 7.1.2.3.

Table 1 Treatment Regimen and Subject Characteristics

Number of Subjects	Treatment Regimen	Characteristics		
		Genotype	Target Allocation	Fibrosis Stage
Total n=250	MK-3682 450 mg + RZR 180 mg for 12 weeks	GT1a	n = 35	F0-F4 (target 25-30% cirrhotic)
		GT1b	n = 15	
		GT2	n = 50	
		GT3	n = 50	
		GT4	n = 50	
		GT5	n = 25	F0-F4
		GT6	n = 25	

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

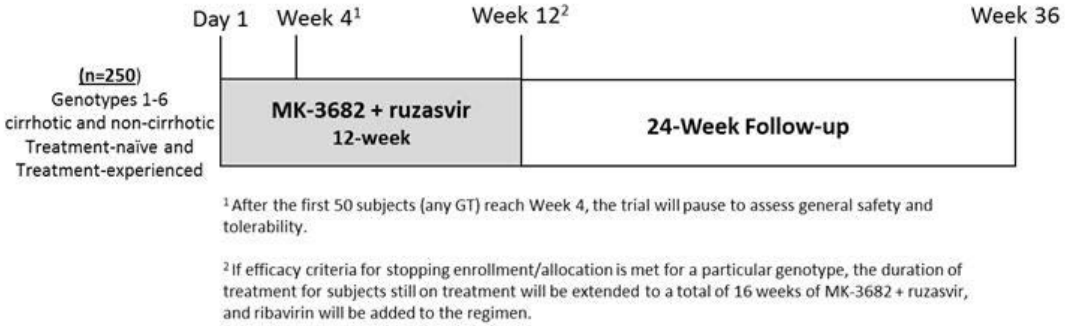

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

As this is an estimation study, there are no formal hypotheses.

Objectives for this study in male and female subjects infected with chronic HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection who are at least 18 years of age are listed in Sections 3.1, 3.2, and 3.3.

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the efficacy of co-administered MK-3682 (450 mg) + RZR (180 mg) as assessed by the proportion of subjects achieving sustained virologic response (SVR) at 12 weeks post-treatment (SVR_{12}) (defined as HCV ribonucleic acid [RNA] <lower limit of quantification [LLOQ] 12 weeks after the end of all study therapy).
2) **Objective:** To evaluate the safety and tolerability of co-administered MK-3682 (450 mg) + RZR (180 mg).

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the efficacy of co-administered MK-3682 (450 mg) + RZR (180 mg) as assessed by the proportion of subjects achieving SVR at 24 weeks post-treatment (SVR_{24}) (defined as HCV RNA <LLOQ 24 weeks after the end of all study therapy).

2) **Objective:** To evaluate the efficacy of co-administered MK-3682 (450 mg) + RZR (180 mg), as assessed by the proportion of subjects experiencing virologic failure (either on-treatment failure or relapse post-treatment) at Follow-up Week (FW) 12 among subjects who do not discontinue study for non–treatment-related (e.g., administrative) reasons.

3) **Objective:** To evaluate the effect of baseline resistance-associated variants (RAVs) in nonstructural protein (NS) 5A and/or NS5B on the efficacy of co-administered MK-3682 (450 mg) + RZR (180 mg), as assessed by the proportion of subjects with baseline RAVs achieving SVR_{12}.

3.3 Exploratory Objectives

1) **Objective**: To evaluate the emergence of NS5A and/or NS5B RAVs in subjects who experience virologic failure.
2) **Objective**: To explore the relationship between genetic variation, including but not limited to variation in IL28B, and response to the treatment administered and mechanisms of disease. Variation across the human genome will be analyzed for association with clinical data collected in this study. See Sections 4.2.5.5, 4.2.5.6, and 12.2.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-3682 and RZR.

Refer to the approved product labeling for detailed background information on RBV.

4.1.1 Pharmaceutical and Therapeutic Background

- MK-3682 is an HCV NS5B polymerase nucleotide inhibitor (NI).
- RZR (ruzasvir, MK-8408) is an HCV NS5A replication complex inhibitor (NS5AI).
- RBV is a nucleoside (ribonucleic analog) inhibitor. For subjects who remain on therapy, RBV will be added to the extended 16-week treatment regimen with MK-3682 + RZR for subjects with a particular GT if efficacy criteria for stopping enrollment/treatment allocation are met for that GT.

4.1.1.1 Overview

The HCV can be divided into 6 GTs. This study will evaluate a novel 2-drug combination regimen to treat subjects with chronic HCV GT1-6 infection. Of the 6 HCV GTs, GT1 and GT3 are the most common, accounting for approximately 46% and 22% of all global infections, respectively. Genotype 1 has a broad geographical distribution, being the most common GT in most of North America, Northern and Western Europe, South America, Asia, and Australia [1]. Genotype 3 is most prevalent in South and Southeast Asia, although migration has resulted in an increased prevalence in Europe and North America. Genotype 2 is the third most common GT worldwide; it has a broad geographical distribution. Genotype 4 is found predominantly in Africa and the Middle East [1] but is increasingly prevalent in the United States and Mediterranean Europe due to migration and increasing transmission through injection drug use [2]. Genotype 5 and GT6 are less common; they predominate in sub-Saharan Africa and in Asia, respectively [1].

With the advent of oral DAAs, effective interferon and ribavirin (RBV)-free combination regimens are now available for subjects chronically infected with certain GTs. However, some subgroups of subjects, particularly treatment-experienced, cirrhotic subjects, do not achieve optimal rates of SVR with existing, approved 12-week regimens. In addition, the currently available dosing regimens are different for different HCV GTs, with some regimens requiring prolonged treatment of up to 24 weeks and/or RBV, thus leading to complexity of treatment. Therefore, a regimen without the efficacy, safety, and convenience deficits of the existing regimen will be a substantial advance in the treatment of HCV infection.

Different approaches can be undertaken to achieve a pangenotypic regimen. Because HCV is an RNA virus capable of substantial mutation in response to targeted antiviral agents, highly efficacious treatments for HCV infection require combinations of DAAs that simultaneously attack multiple points of the viral replication cycle. Effective therapies can differ with respect to the number of DAAs included in a regimen, doses of the individual agents, treatment duration, and/or inclusion of RBV.

Merck is evaluating 2 regimens with potentially pangenotypic activity.

The first regimen consists of 3 drugs: an NS3/4A inhibitor (grazoprevir, GZR), an NS5A inhibitor (RZR), and an NS5B inhibitor (MK-3682). MK-3682B, a fixed-dose combination (FDC) of MK-3682 (450 mg)/GZR (100 mg)/RZR (60 mg), is being evaluated in 3 ongoing Phase 2 trials (MK-3682 Protocol Number [PN]011, MK-3682 PN012, and MK-3682 PN021). Studies in treatment-naïve and or prior-peginterferon/RBV treatment failures have enrolled 609 GT1, GT2, GT3, and GT4-infected subjects. The studies have investigated 8-, 12-, or 16-week regimens of MK-3682B administered with or without RBV (see Section 4.1.2.2). MK-3682B is also being evaluated as a treatment for patients who have failed all-oral, IFN-free DAA regimens.

Because MK-3682 and RZR are potent antiviral agents that inhibit the HCV NS5B RNA polymerase and NS5A replication complex, respectively, the combination of these 2 DAAs may be a highly effective regimen. This combination is currently being evaluated in MK-3682 PN035, an ongoing Phase 2 study characterizing the efficacy and safety profile of a 12-week regimen of MK-3682 450 mg + RZR at a dose of 60 mg. Dosing in PN035 is ongoing, and efficacy results are not yet available.

In studies of NS5A-inhibitor containing regimens (SOF/VEL, SOF/DCV, EBR/GZR), presence of certain substitutions in the NS5A gene prior to initiation of therapy can reduce efficacy; furthermore, patients who fail therapy often have treatment-emergent substitutions that confer resistance to NS5A inhibitors [3] [4] [5] [6] [7] [8] [9] [10]. Hence, it was of interest to evaluate whether administration of regimens that include higher doses of NS5A inhibitors could result in higher efficacy by overcoming baseline or treatment-emergent NS5A inhibitor resistant virions. Such an approach is aided by the generally excellent safety profile of NS5A inhibitors developed to date. PN041 is designed to evaluate this type of regimen. In particular, PN041 will explore a regimen consisting of MK-3682 450 mg + RZR 180 mg. In this regimen, the dose of RZR is 3-fold higher than that being tested in PN035 (MK-3682 450 mg + RZR 60 mg) and in the PN011/PN012/PN021 (MK-3682 450 mg + RZR 60 mg + GZR 100 mg).

The preclinical and clinical profiles of MK-3682 and RZR demonstrate high potency against GT1-6 *in vitro*, supporting the use of this 2-drug combination in this trial (see Section 4.2.2). MK-3682 is at least equipotent to sofosbuvir (SOF), an approved NS5B inhibitor that anchors multiple current all-oral DAA therapies. In *in vitro* replicon studies, RZR is more potent against multiple HCV GTs and resistant variants compared with other NS5A inhibitors, such as the approved drugs ledipasvir (LDV), daclatasvir (DCV), ombitasvir (OMB), elbasvir (EBR), and velpatasvir (VEL). Therefore, a regimen that combines MK-3682 and RZR may be sufficient to result in high efficacy in clearing HCV infection of all GTs. The rationale for the subject population, study design, doses of each of the compounds, and the duration of therapy are provided in subsequent sections.

4.1.1.2 Current Treatment of Chronic HCV

Phase 2 or 3 trials have evaluated the efficacy of several all-oral, IFN-free regimens administered for 12 weeks in GT1-6-infected subjects. As displayed in Table 2, treatment outcomes with the various approved and investigational DAA regimens have SVR_{12} rates

ranging from 58% to 100%. Some of these regimens are suboptimal in that they require use of RBV, and there is a risk of relapse among subjects with baseline NS5A RAVs.

As previously introduced in Section 4.1.1.1 and detailed in Section 4.1.2.2, MK-3682B, an FDC of MK-3682 (450 mg)/GZR (100 mg)/RZR (60 mg), is currently being evaluated in 3 ongoing Phase 2 trials (MK-3682 PN011, MK-3682 PN012, and MK-3682 PN021) in GT1-6-infected subjects for 8- to 24-week durations with or without RBV. Preliminary data from these studies demonstrate excellent tolerability and very high efficacy of this 3-drug regimen when administered for 8 or 12 weeks in GT1- and GT3-infected subjects and for 12 weeks in GT2-infected subjects.

Table 2 Efficacy of Approved and Investigational 12-Week DAA Regimens for Treatment-Naïve Non-Cirrhotic and Cirrhotic Subjects

GT	Regimen	Non-cirrhotic (% SVR_{12})	Cirrhotic (% SVR_{12})	Reference
Approved 12-Week Regimens for GT1				
1	LDV/SOF	94%-99%	94%	[11] [12] [13] [14] [15]
	SOF/VEL	98%	99%	[3]
	Dasabuvir/ombitasvir/paritaprevir/ritonavir + RBV	96%	92%	**[16] [17] [18]**
	EBR/GZR	94%	98%	**[4] [5] [6]**
Experimental 12-Week Regimens for GT1				
1	ABT493/ABT530	100%	96%	**[19] [20]**
Approved 12-Week Regimens for GT2				
2	SOF+RBV (FISSION, POSITRON, and VALENCE studies)	94%[a]	94%[a]	**[21] [22] [23]** [24]
	SOF/VEL	99%-100%[b]	99%-100%[b]	**[3] [25]**
Approved 12-Week Regimens for GT3				
3	SOF+RBV	~80-85%[a]	~80-85%[a]	[24]
	SOF/daclatasvir (DCV)	92-98%	58-69%	**[7] [8] [9]** [10]
	SOF/VEL	97%	91%	[25]
Experimental 12-Week Regimens for GT3				
3	ABT493/ABT530	97%	100%	[19] [20]

GT	Regimen	Non-cirrhotic (% SVR_{12})	Cirrhotic (% SVR_{12})	Reference
Approved 12-Week Regimens for GT4				
4	LDV/SOF	93%	100%	[26]
	SOF/VEL	100%	100%	[3]
	Ombitasvir/paritaprevir/ritonavir + RBV	100%	No data	**[18] [27] [28]**
	EBR/GZR	96%	100%	**[4] [5] [6]** [29]
Experimental 12-Week Regimens for GT4				
4	ABT493/ABT530	100%	No data	[30]
Approved 12-Week Regimens for GT5				
5	LDV/SOF	97%	89%	**[13] [31]**
	SOF/VEL	97%	100%	[13] [31]
Approved 12-Week Regimens for GT6				
6	LDV/SOF	96%[b]	96%[b]	**[13] [32]**
	SOF/VEL	100%	100%	[3]

EBR = elbasvir; GZR = grazoprevir; LDV = ledipasvir; RBV = ribavirin; SOF = sofosbuvir; SVR=sustained virologic response; VEL = velpatasvir.
[a] Cirrhotic state was not specified.
[b] Value represents combined data from subjects with and without cirrhosis.

4.1.2 Background on Drugs Used in this Trial

Background data is provided for MK-3682 and RZR. Refer to the MK-3682 and RZR IBs for more information on the preclinical and clinical studies with these drugs. Summaries of ongoing clinical trials are provided in Sections 4.1.2.1 and 4.1.2.2.

Refer to the product label for background information on RBV.

4.1.2.1 Phase 1 Studies

MK-3682 and RZR are currently being evaluated in multiple ongoing Phase 1 trials. Please refer to the MK-3682 and RZR IBs for more detailed information on the Phase 1 clinical studies with MK-3682 and RZR.

MK-3682 has been generally well-tolerated in healthy subjects and HCV-infected subjects in several Phase 1 clinical studies at single doses up to 900 mg, multiple doses up to 750 mg per day for 10 days, and in Phase 2a trials of 300 mg or 450 mg once daily for up to 24 weeks.

RZR has been generally well-tolerated in subjects in 8 RZR Phase 1 trials and in over in ongoing Phase 2a trials. RZR has been administered at doses up to 600 mg/day (10 times the proposed clinical dose), 100 mg given daily for 10 days, and 60mg once daily for up to 24 weeks.

4.1.2.2 Summary of Ongoing Phase 2 Clinical Trials

MK-3682 and RZR are currently being evaluated in combination with GZR. The combination of GZR with EBR, a first generation NS5A inhibitor (EBR/GZR, ZEPATIER™), was recently approved in the United States (US), Canada, European Union, and other countries for the treatment, with or without RBV, of chronic HCV GT1 or GT4 infection in adults. A fixed-dose combination tablet of MK-3682/GZR/RZR (MK-3682B) is currently being evaluated in 3 ongoing Phase 2 trials (MK-3682 PN011, MK-3682 PN012, and MK-3682 PN021) in GT1-6-infected subjects for 8- to 24-week durations with or without RBV. Brief summaries of the Phase 2 three-drug combination regimen studies containing MK-3682 and RZR are provided in Sections 4.1.2.2.1 and 4.1.2.2.3.

4.1.2.2.1 MK-3682 PN011 and PN012

4.1.2.2.1.1 Part A

In Part A of MK-3682 PN011 and PN012, 93 GT1 (46 GT1a, 47 GT1b), 61 GT2, and 86 GT3-infected TN, non-cirrhotic subjects with chronic HCV infection were dosed once-daily for 8 weeks' duration with 1 of 4 regimens including MK-3682 (300 mg or 450 mg), GZR (100 mg), and either EBR (50 mg) or RZR (60 mg).

All regimens were highly efficacious in subjects infected with GT1. No subject experienced virologic breakthrough on therapy. Across treatment arms, 45/46 (98%) GT1a and 46/47 (98%) GT1b subjects achieved SVR_{12}. There was no observed impact of NS5A RAVs (defined as any change from wild-type at 9 positions [24, 28, 30, 31, 32, 38, 58, 92, or 93]); 23% of subjects had baseline NS5A RAVs, and all achieved SVR_{12}. No treatment-emergent RAVs were observed.

In subjects infected with GT2, the MK-3682 (450 mg)/GZR/RZR regimen was highly effective (94%), but SVR rates were suboptimal among subjects who received the other regimens (60% to 71%). The MK-3682 (450 mg)/GZR/RZR regimen achieved SVR_{12} among 94% (15/16) of GT2-infected subjects, despite a high prevalence of baseline NS5A RAVs (defined as any change from wild-type at 9 positions [24, 28, 30, 31, 32, 38, 58, 92, or 93]) in 94% (15/16) subjects. No treatment-emergent RAVs were observed.

All regimens were highly efficacious in subjects infected with GT3. Overall, 38/43 (88%) of subjects who received EBR and 40/43 (93%) of subjects who received RZR achieved SVR_{12}. The MK-3682 (300 mg or 450 mg)/GZR/RZR regimens achieved SVR_{12} among 93% (40/43) of GT3-infected subjects, despite baseline NS5A RAVs (defined as any change from wild-type at 10 positions [24, 28, 30, 31, 32, 38, 58, 62, 92, or 93]) in 47% (20/43) of subjects. One of the 3 relapsers in these arms had a treatment-emergent NS5A RAV (Y93H) at the time of failure.

All 240 subjects completed the full 8 weeks of dosing. All regimens were generally well tolerated, and no cardiac or renal safety signals were identified. The frequency and severity of adverse events (AEs) were comparable among the 4 treatment groups. The most frequent study drug-related AEs were headache (23%), fatigue (20%), and nausea (13%). One subject (1/240, 0.4%) experienced an alanine aminotransferase (ALT) increase >5× upper limit of normal (ULN) at Treatment Week (TW) 8 with a pattern consistent with the late ALT increases observed in the Phase 2 and 3 GZR studies, which rapidly resolved off study drug.

There were no drug-related serious adverse events (SAEs) and no subjects discontinued due to AEs.

4.1.2.2.1.2 Part B

The results of Part A demonstrated that an 8-week regimen of MK-3682/GZR/RZR (450 mg/100 mg/60 mg) was highly effective and well-tolerated in GT1-, GT2-, and GT3-infected TN, non-cirrhotic subjects, supporting the selection of this regimen from the 4 tested in Part A for further evaluation among a diverse population of HCV-infected subjects, including those with additional HCV GTs, cirrhosis, prior treatment, and HIV/HCV-co-infection.

In Part B of these studies, the combination regimen is being administered as FDC tablets, referred to as MK-3682B. Each MK-3682B tablet contains MK-3682 (225 mg), GZR (50 mg), and RZR (30 mg), and is administered as 2 tablets once daily, for a total daily dose of MK-3682 450 mg, GZR 100 mg, and RZR 60 mg. Non-cirrhotic and cirrhotic, TN and pegylated IFN/RBV (PR) treatment-experienced, GT1-GT6 subjects with or without HIV co-infection were planned to receive MK-3682B with or without RBV for 8, 12, or 16 weeks of therapy, depending on the treatment arm.

As of 25 July 2016, 609 subjects have been enrolled in Part B: 153 GT1-infected (82 GT1a, 71 GT1b) TN subjects with or without compensated cirrhosis, 135 GT2 TN subjects with or without cirrhosis, and 315 GT3-infected TN or TE (PR) subjects with or without compensated cirrhosis. Subjects were treated with MK-3682B, with or without RBV, for 8, 12, or 16 weeks. Subjects could be mono-infected or HIV co-infected. Six subjects infected with GT4 have been enrolled, but results are not yet available for this genotype.

Results to date for GT1, GT2, and GT3-infected subjects are available (see Table 3). One hundred twenty-six GT1-infected subjects have reached at least FW4. All subjects had undetectable HCV RNA at the end of 8 or 12 weeks of treatment. Of 41 subjects (19 GT1a, 22 GT1b) who received 8 weeks of therapy and who have reached FW4, 100% (41/41) have achieved SVR_4. Fifteen subjects were cirrhotic (2 GT1a/13 GT1b). Of 85 subjects (46 GT1a/39 GT1b) who received 12 weeks of therapy and who have reached FW4, 100% (85/85) have achieved SVR_4. Thirty-eight subjects were cirrhotic (17 GT1a/21 GT1b). Baseline next-generation sequencing (NGS) (15% sensitivity threshold) is available for 92 subjects; 7.8% (4/51) GT1a and 26.8% (11/41) GT1b subjects had baseline NS5A RAVs at positions 30, 31, and 93.

Of the GT2-infected subjects, 117 have ≥4 weeks of post-therapy follow-up (Table 3). Among all participants, 134/135 (99%) subjects had HCV RNA <LLOQ at the end of their assigned 8, 12, or 16 weeks of treatment. One cirrhotic subject who was randomized to 12 weeks of MK-3682B + RBV had an HCV RNA that was 279 IU/mL at TW 12, despite being <LLOQ since TW2; HCV RNA was subsequently undetectable at FW4 and FW8. Compensated cirrhotic subjects were randomized to 12 or 16 weeks of treatment. Of the 117 subjects who have reached at least FW4, 39/45 (87%) of those assigned to 8 weeks of treatment (with or without RBV) have achieved SVR_4+ and 71/71 (100%) of those assigned 12 or 16 weeks of treatment (with or without RBV) have achieved SVR_4+. Of note, SVR_4+ was achieved for 100% (40/40) of cirrhotic subjects for whom data are available at this time. SVR_4+ rates are comparable between arms of the same duration with or without RBV. In the

8-week arms, failures are associated with detection of baseline substitutions at NS5A amino acid 31. Such substitutions are associated with an approximately 4-fold reduction in the potency of RZR *in vitro*. Baseline NGS (15% sensitivity threshold) is currently available for 35 of the 47 subjects receiving 8 weeks of treatment ± RBV; 43% (15/35) of subjects had NS5A L31M at baseline. SVR_4+ for subjects with baseline L31M is 73% (11/15); for subjects with baseline 31L, SVR_4+ is 95% (19/20).

Of the GT3-infected subjects, 283 have reached at least FW4 (Table 3). All subjects had undetectable HCV RNA at the end of their assigned 8, 12, or 16 weeks of treatment. Of the 283 subjects (189 non-cirrhotic, 94 cirrhotic) who have reached FW4, 98% (276/283) have achieved SVR_4. SVR_4 rates are comparable between different durations of treatment, arms with and without RBV, and between non-cirrhotic and cirrhotic subjects and those with or without prior PR treatment-experience. Baseline NGS (15% sensitivity threshold) is available for 145 subjects; 18.5% (23/124) GT3 subjects had baseline NS5A RAVs at positions 30, 31, and 93. SVR (last visit on record) for subjects without baseline RAVs at positions 30, 31, or 93 is 99% (121/122); for subjects with baseline RAVs, SVR_4+ is 20/23 (87%).

Table 3 Preliminary results for PN011 and PN012 Part B for 8, 12 or 16 weeks of MK-3682B with or without RBV in GT1-, GT2-, and GT3-infected Subjects With and Without Cirrhosis; % of Subjects Achieving SVR_4+ of Those Who Have Reached at least FW4 (as of 05 June 2016)

Regimen	**Non-Cirrhotic[1] n/N (% SVR)**	**Cirrhotic[1] n/N (% SVR)**	**Total[1] n/N (% SVR)**
GT1a 8 weeks	17/17 (100%)	2/2 (100%)	19/19 (100%)
GT1b 8 weeks	9/9 (100%)	13/13 (100%)	22/22 (100%)
GT1a 12 weeks	29/29 (100%)	17/17 (100%)	46/46 (100%)
GT1b 12 weeks	18/18 (100%)	21/21 (100%)	39/39 (100%)
GT2 8 weeks	14/16 (88%)	--	14/16 (88%)
GT2 8 weeks, RBV	25/29 (86%)	--	25/29 (86%)
GT2 12 weeks	31/31 (100%)	10/10 (100%)	41/41 (100%)
GT2 12 weeks, RBV	--	10/10 (100%)	10/10 (100%)
GT2 16 weeks	--	21/21 (100%)	21/21 (100%)
GT3 8 weeks	TN: 15/16 (94%) TE: 15/15 (100%)	--	30/31 (97%)
GT3 8 weeks, RBV	TN: 35/35 (100%) TE: 13/14 (93%)	--	48/49 (98%)
GT3 12 weeks	TN: 34/35 (97%) TE: 14/14 (100%)	TN: 13/14 (93%) TE: 9/9 (100%)	70/72 (97%)
GT3 12 weeks, RBV	TN: 35/35 (100%) TE: 13/14 (93%)	TN: 15/15 (100%) TE: 9/9 (100%)	72/73 (99%)
GT3 16 weeks	TE: 10/11 (91%)	TN: 10/10 (100%) TE: 17/17 (100%)	37/38 (97%)
GT3 16 weeks, RBV	--	TE: 19/20 (95%)	19/20 (95%)

C = cirrhotic; GT = genotype; NC = noncirrhotic; RBV = ribavirin; SVR = sustained virologic response; TE = treatment experienced; TN = treatment naïve.
[1] $SVR_{4/8/12}$ (last visit on record) in subjects with ≥4 weeks of post-therapy follow-up, as of 05 June 2016.

Treatment in Part B was generally well tolerated. There were no observed cardiac or renal safety signals. One GT1-infected patient died due to a bacterial sepsis considered unrelated to study drug. The most frequent study drug-related adverse events in >5% of all patients in all study arms were fatigue, headache, and nausea.

The results to date suggest that MK-3682B for 8 or 12 weeks is effective and well tolerated in GT1-infected treatment-naïve, non-cirrhotic, and cirrhotic patients, and MK-3682B for 12 weeks is effective and well tolerated in GT2-infected treatment-naïve, non-cirrhotic and compensated cirrhotic subjects, and MK-3682B for 8 or 12 weeks is effective and well-tolerated in GT3-infected treatment-naïve or treatment-experienced, non-cirrhotic and cirrhotic patients. Addition of RBV to a 12 week regimen did not appear to improve efficacy.

4.1.2.2.1.3 Part C

Part C of PN011 and PN012 is evaluating a re-treatment regimen for subjects in Part A who failed therapy. GT1-, GT2-, and GT3-infected initially TN non-cirrhotic subjects who relapsed after 8 weeks of therapy with any of the 4 regimens in Part A were offered re-treatment with 16 weeks of MK-3682B plus RBV. Twenty-four of 26 eligible subjects were enrolled, 2 with GT1, 14 with GT2, and 8 with GT3 infection. At the time of relapse following initial therapy, NS5A RAVs were detected in 0% (0/2) GT1, 93% (13/14) GT2, and 88% (7/8) GT3 subjects. NS3 RAVs were detected in 50% (1/2) GT1, 100% (14/14) GT2, and 100% (8/8) GT3 subjects. NS5B RAVs were detected in 50% (1/2) GT1, 0% (0/14) GT2, and 0% (0/8) GT3 subjects, and 88% (21/24) subjects had RAVs in >1 class. One GT2-infected patient withdrew after a single dose with AEs of vomiting and tachycardia considered related to MK-3682B + RBV. One GT2-infected patient discontinued RBV 4 days before the scheduled completion of 16 weeks of therapy due to an AE of rash thought to be RBV-related. This subject completed 16 weeks of MK-3682B. The remaining 22 subjects completed the full 16 weeks of dosing.

All subjects had undetectable HCV RNA at the end of treatment. All 23 subjects (2 GT1, 13 GT2, and 8 GT3) have reached at least FW4; 100% have achieved SVR_4. As of 22 July 2016, 20 subjects (2 GT1, 10 GT2, and 8 GT3) have reached FW12; 100% have achieved SVR_{12}. Treatment was generally well tolerated, and no cardiac or renal safety signals were identified. The most frequent study drug-related AEs in >10% of all subjects were headache, fatigue, nausea, rash, pruritus, insomnia, decreased hemoglobin, and cough. The study results to date suggest that a 16-week regimen of MK-3682B plus RBV is effective and well-tolerated in GT1, GT2, and GT3-infected non-cirrhotic subjects who had previously failed 8 weeks of treatment with a 3-drug regimen, despite a high prevalence of baseline NS3 and NS5A RAVs.

4.1.2.2.2 MK-3682 PN021

MK-3682 PN021 is an ongoing Phase 2 randomized, multicenter, open-label trial to evaluate the safety and efficacy of MK-3682B for 16 weeks with RBV or 24 weeks without RBV in non-cirrhotic and compensated cirrhotic subjects with GT1 infection who have failed a previous DAA regimen. A subsequent cohort will enroll GT3 patients. Ninety-four GT1 patients have been randomized in this trial (80 [85%] GT1a; 14 [15% GT1b]). Patients had failed >8 weeks of ledipasvir/SOF (59 [63%]), ≤8 weeks of LDV/SOF (13 [14%]) or EBR/GZR (22 [23%]). Forty patients (43%) had cirrhosis. As of 21-July-2016, of the 94 enrolled subjects 2 have discontinued and 33 have completed treatment; all 92 subjects who have reached TW8 have achieved undetectable HCV RNA on treatment. To date, 22 subjects in the 16 week/RBV arm have reached FW4; all have achieved SVR4 (Table 4).

Table 4 Current Efficacy Results for PN021

Proportion of Patients with HCV RNA <15 IU/mL [n/m, (%)]		
Treatment Week 4	Treatment Week 8	SVR4 (16 weeks/RBV)
85/92 (92%)	92/92 (100%)	22/22 (100%)

4.1.2.2.3 MK-3682 PN035

MK-3682 PN035 is an ongoing Phase 2 study that is currently evaluating the efficacy and safety profile of a 12-week regimen of MK-3682 450 mg + RZR 60 mg among subjects infected with GT1-6. As of 11-July-2016, 122 subjects have started treatment. All subjects have had rapid suppression of HCV viral loads and there have been no virologic breakthroughs on treatment.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Currently approved HCV IFN-free DAA regimens, such as LDV/SOF, SOF/VEL, ombitasvir/paritaprevir/dasabuvir/ritonavir+RBV, and EBR/GZR, have better efficacy, tolerability, and convenience than earlier therapies. However, they are not uniformly effective across the 6 HCV GTs. The most effective regimens are for GT1 HCV, which accounts for approximately 46% of infections worldwide [1]. Genotypes 2 and 3 HCV, the next most common GTs, were historically grouped together in treatment guidelines. However, recent studies have shown that infection with GT3, especially in subjects with cirrhosis, is more difficult to treat **[25] [8] [9]**. In addition, although GT5 and GT6 have a more limited geographic distribution than GT1-4, they predominate in certain regions of the world and represent an unmet medical need with limited clinical experience. In addition, even though several IFN-free combinations are now available for treatment of HCV, clinicians must still take into account the GT and even the subtype, as well as patterns of antiviral resistance in the choice of a regimen. The development of a single, uniform, and pangenotypic regimen that will be safe and effective in all patient populations would represent a substantial advance in the treatment of HCV infection by greatly simplifying treatment paradigms and reducing the need for pretreatment testing and on-treatment monitoring. The clinical potential of the combination of MK-3682 and RZR, both once-daily medications, is suggested by their non-overlapping viral targets, the pangenotypic *in vitro* potencies of both MK-3682 and RZR, the proven success of other HCV NIs in combination with other NS5A inhibitors, and the high efficacy rates from the investigational 3-drug regimen containing MK-3682, GZR, and RZR.

As previously described in Section 4.1.2, the investigational 3-drug regimen containing MK-3682, RZR, and GZR is being explored as a strategy to use 3 DAA agents, each directed at a different target of the hepatitis virus life cycle. As part of a comprehensive clinical development program, the combination of MK-3682 and RZR is currently being evaluated in MK-3682 PN035, an ongoing Phase 2 study characterizing the efficacy and safety profile of MK-3682 at a dose of 450 mg and RZR at a dose of 60 mg for 12 weeks duration. Dosing in PN035 is ongoing, and efficacy results are not yet available. PN041 is designed to explore

RZR at a dose of 180 mg as part of the 2-drug DAA regimen of MK-3682 (450 mg) and RZR (180 mg). The purpose of PN041 is to evaluate the use of a higher dose of RZR as a potential strategy to develop a highly efficacious pangenotypic DAA regimen for the treatment of chronic HCV. The rationale for dose selection is provided in Section 4.2.4.2.

4.2.2 Rationale for the Selected Subject Population

The rationale for the population selected for this trial is as follows:

- **Genotype:** The efficacy of the 2-drug regimen in subjects with chronic HCV-GT1-6 will be evaluated to allow for an initial assessment of the 2-drug combination regimen of MK-3682 and RZR as a pangenotypic therapy for HCV. The preclinical profiles of MK-3682 and RZR demonstrate high potency against GT1-6 *in vitro*. In addition, the preliminary data from Phase 2 studies of MK-3682/GZR/RZR demonstrate excellent tolerability and high efficacy of this 3-drug regimen when administered in GT1, GT2, and GT3. Taken together, these data support the clinical evaluation of the combination of MK-3682 and RZR as a pangenotypic therapy for HCV.

  In preclinical *in vitro* experiments, MK-3682 and RZR were shown to have high potency against all GTs.

  - The triphosphate of MK-3682, MK-3682-NTP, is a potent, pangenotypic inhibitor of HCV NS5B polymerase, with mean IC_{50} values of 0.144 ± 0.011 μM (GT1a), 0.238 ± 0.024 μM (GT1b), 0.250 ± 0.005 μM (GT2a), 0.156 ± 0.012 μM (GT3a), 0.149 ± 0.016 μM (GT4a), 0.233 ± 0.003 μM (GT5a), and 0.097 ± 0.006 μM (GT6a).
  - RZR is a potent, pangenotypic inhibitor of NS5A, with low EC_{90} against GT1a (0.002 nM), GT1b (0.003 nM), GT2a (0.001 nM), GT2b (0.036 nM), GT3a (0.006 nM), GT4a (0.011 nM), GT5a (0.001 nM) and GT6 (0.004 nM) in replicon assays.

- **Treatment-Naïve:** TN subjects who have never received medical therapy for HCV and have no evidence of cirrhosis represent the largest proportion of the HCV-infected population worldwide. Historically, these subjects have had a high response rate to HCV DAA therapies.

- **Treatment-Experienced Subjects**: This study will also include subjects who have previously failed treatment with IFN-based therapies, because subjects who have failed prior interferon-based treatment are among the populations at highest need for effective HCV treatments. Although the efficacy rates in IFN-based TE populations have historically been lower than in TN populations, more recent IFN-free DAA therapies combining highly potent drugs have demonstrated high rates of SVR_{12} in TE subjects that are comparable to those achieved in TN subjects **[12] [15] [3]** [22] [33] [25] [34]. Given the comparable SVR_{12} rates observed following some all-oral DAA regimens in TE and TN subjects, TE subjects will be permitted to enroll in this study. As stated in Sections 2.1 and 4.2.3, this study includes duration modification rules to limit the potential for subjects to be at risk for virologic failure. Subjects who have failed prior DAA regimens will not be included in this study to allow further

evaluation of the efficacy of this 2-drug regimen in TN and PR TE subjects, some of whom will have baseline RAVs. The DAA failure population may have a higher prevalence of baseline RAVs so is best addressed at a later time.

- **Non-cirrhotic Subjects**: Non-cirrhotic subjects represent a large proportion of the HCV-infected population worldwide. Historically, these subjects have had a high response rate to HCV DAA therapies.

- **Compensated Cirrhotic Subjects:** Subjects with cirrhosis who are at increased risk for progression to decompensated cirrhosis and liver complications are one of the more challenging groups in need of new therapeutic approaches. Although the efficacy rates in cirrhotic populations have historically been lower than in non-cirrhotics, requiring longer treatment durations or the addition of RBV to achieve equivalent SVR rates, more recent IFN-free DAA therapies combining highly potent drugs have demonstrated rates of SVR_{12} in compensated cirrhotic subjects that are comparable with those achieved in non-cirrhotic subjects **[4] [3] [25]** [34]. Given the comparable SVR_{12} rates observed following 12 weeks of all-oral IFN-free DAA regimens in non-cirrhotic and compensated cirrhotic subjects, including the 3-drug regimen of MK-3682/GZR/RZR in non-cirrhotic and compensated cirrhotic subjects, subjects with compensated cirrhosis will be permitted to enroll in this study. In addition, as stated in Sections 2.1, 4.2.3, and 5.11, this study includes limitations on the number of cirrhotics, stopping rules, and duration modification rules to limit the potential for subjects to be at risk for virologic failure. Subjects with advanced or decompensated cirrhosis will not be included in this study.

- **HIV Co-infected Subjects:** HIV co-infected subjects are included in this trial because HCV infection is a leading cause of morbidity and mortality among those with HIV-1 [35]. Compared to the general population, the overall prevalence of HCV infection is higher among those infected with HIV-1. In fact, one-fourth to one-third of subjects infected with HIV in the US and Europe are co-infected with HCV [36]. Compared to subjects infected with HCV alone, HIV/HCV co-infected subjects have higher baseline HCV viral loads (VLs) and more rapid progression of liver disease, including more rapid hepatic fibrosis as well as an increased risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Subjects with HIV/HCV co-infection are also more susceptible to developing anemia, and they may have more rapid progression to acquired immunodeficiency syndrome (AIDS) and AIDS-related death [29]. Recent DAA therapies have demonstrated rates of SVR_{12} that are comparable with those achieved in HCV disease-matched mono-infected subjects. In particular, HIV subjects co-infected with HCV GT1 or GT4 had similarly high efficacy following EBR/GZR therapy in Phase 3 studies compared to those who were not HIV-infected [6]. Given the comparable SVR_{12} rates observed following all-oral IFN-free DAA regimens in mono-infected and co-infected subjects, HIV/HCV co-infected subjects will be permitted to enroll in this study. A comprehensive set of drug-interaction trials has defined the antiretroviral therapies that can be co-administered with MK-3682, GZR, and RZR (Section 5.5).

4.2.3 Rationale for Study Design

The pangenotypic preclinical profiles of MK-3682 and RZR, as well as the preliminary efficacy results from the 3-drug, 8- and 12-week regimens of MK-3682/GZR/RZR in GT1, GT2, and GT3 support the proposed evaluation in this protocol of the safety and efficacy of MK-3682 + RZR in TN or prior IFN-based TE, non-cirrhotic and compensated cirrhotic GT1-, GT2-, GT3-, GT4-, GT-5, and GT-6-infected subjects. A treatment duration of 12 weeks for all GTs using the MK-3682 + RZR combination in this study is supported by the equipotent or superior *in vitro* potency profiles of MK-3682 and RZR (Section 4.2.2) compared to other compounds of the same classes, such as the approved NI/NS5A regimens of LDV/SOF and SOF/VEL, that have demonstrated high efficacy rates against GT1-6 after 12 weeks of treatment as 2-drug IFN-free DAA regimens. Ribavirin is not proposed to be evaluated in this trial given the high efficacy rates observed with other 2-drug all-oral DAA regimens without RBV, such as LDV/SOF and SOF/VEL, and the equipotent or superior in vitro potency profiles of MK-3682 and RZR compared to these regimens.

Since this is an estimation study, no comparator or placebo is used. No statistical comparisons are planned for efficacy and safety data. A target number of GT1-, GT2-, GT3-, and GT4-infected subjects are specified in order to provide sufficient confidence of the estimated treatment response rate in these GTs, since they are the most prevalent GTs globally. Since subjects with GT5 and GT6 are uncommon outside of certain geographic areas, the study will enroll approximately a stated number of subjects with the assumption that full enrollment of these GTs may not be reached.

Treatment allocation will pause after the first 50 subjects complete the TW4 visit. This will allow general safety and tolerability to be assessed after these first 50 subjects complete TW4, an assessment of 20% of the overall allocation target. The TW4 time point allows for steady state of drug to be achieved for ≥2 weeks. The criteria described in Section 5.11.1 provide a conservative approach to expanding treatment allocation to the subsequent 200 subjects. These criteria will allow the identification of safety concerns, while not allowing the trial to be stopped unnecessarily.

Treatment allocation may be stopped or paused at any time during the trial if certain criteria are met, as detailed in Section 5.11. If efficacy criteria for stopping enrollment/treatment allocation are met (Section 5.11.4), then no additional subjects of that particular GT will be allocated to treatment in the trial. In addition, the treatment regimen will be modified for all subjects of that GT still on treatment by extending the duration of treatment with MK-3682 + RZR to 16 weeks and adding RBV to the regimen.

4.2.4 Rationale for Dose Selection/Regimen

4.2.4.1 Dose Selection for MK-3682

The 450-mg dose of MK-3682 was chosen for the MK-3682B FDC regimen based on the dose-response analysis generated by monotherapy data from MK-3682 PN001, by the exposure data from the tablet formulation from MK-3682 PN003 and by dose ranging data from PN011 and PN012 Part A. This analysis suggests that the 450-mg dose of MK-3862 in the tablet formulation will be well on the plateau of the dose-response curve and would

provide improved protection against loss of efficacy than would the 300 mg of the tablet formulation, while still maintaining margins to preclinical safety exposures. Efficacy of the MK-3682 300 mg and 450 mg dose arms in GT3-infected subjects in PN012 Part A showed SVR_{12} of 39/42 (93%) and 39/44 (89%), respectively. In GT2-infected subjects in MK-3682 PN011 Part A, slightly higher efficacy was observed in subjects on the 450-mg dose of MK-3682, with an SVR_{12} rate of 77% (24/31) versus 70% (21/30) on the 300-mg dose. The highest efficacy in GT2-infected subjects was observed in the MK-3682 (450 mg)/GZR/RZR arm with an SVR_{12} rate of 94% (15/16), supporting the selection of this regimen for Part B. In addition, the 450-mg dose of MK-3682 has demonstrated an acceptable safety profile when administered once daily for up to 24 weeks in Phase 2 studies, with no difference compared with the 300 mg dose. Therefore, 450 mg was selected as the dose to be evaluated in this protocol.

4.2.4.2 Dose Selection for RZR

Based on the available safety, tolerability, PK, and PD data, 180 mg and 60 mg doses of RZR, respectively, were chosen to be evaluated in combination with a 450 mg dose of MK-3682 in this protocol and in the ongoing PN035.

Preliminary PD data from RZR PN003 have demonstrated that 60 mg of RZR monotherapy for 5 days achieved >3 log_{10} mean maximal viral load reduction in HCV GT1-, GT2-, and GT3-infected subjects. Additionally, the efficacy was similar across doses of 10- to 60-mg doses. The mean maximum VL reduction was -3.82 in GT2 and -2.83 in GT3 following 10 mg of RZR for 5 days, and -3.03 in GT3 following 30 mg of RZR for 5 days. However, a less robust VL reduction (-1.75 log_{10} IU/mL) at a 120-mg dose was observed in GT3-infected subjects due to baseline or treatment-emergent RAVs in the 3 GT3-infected subjects. One subject had S62L/Y93H RAVs at baseline and a treatment-emergent maximal VL reduction of -0.34 log_{10} IU/mL; 1 subject had no detectable RAVs at baseline but had both S62L and Y93H treatment-emergent RAVs and a -1.85 log_{10} IU/mL VL reduction; and the third subject had an A30K RAV at baseline and a Y93H/Y treatment-emergent RAV and -3.06 log_{10} IU/mL VL reduction. The results from monotherapy study suggested that RZR at a dose of equal or greater than 10 mg is associated with a robust VL decline, but RZR monotherapy may not exhibit full efficacy against some GT3 RAVs and therefore supports the further evaluation of RZR at a dose equal to or greater than 10 mg in combination with other antiviral agents. For detailed information, please refer to the RZR IB.

The high efficacy rates from the Phase 2 studies of the 3-drug regimen containing MK-3682 450 mg, RZR 60 mg, and GZR 100 mg in GT1-, GT2, and GT3-infected subjects support the continued development of the MK-3682B regimen with a 60-mg dose of RZR. PN035 is currently being conducted to evaluate the 2-drug regimen of MK-3682 (450 mg) and RZR (60 mg).

Given that GZR is highly effective in GT1-infected subjects, it is possible that a higher dose of RZR may be needed to compensate for the removal of GZR in a 2-drug regimen. The current study (evaluating RZR 180 mg) is proposed to examine the dose response of RZR in combination with MK-3682 as a potential highly efficacious 2-drug regimen.

The higher dose of RZR selected for this trial, 180 mg, is supported by the preclinical safety margin and the predicted PK. RZR at the 60-mg dose has demonstrated excellent tolerability

when administered alone or as an MK-3682B FDC regimen in combination with MK-3682 and GZR (Section 4.1.2.2.1). The steady state exposures of RZR 180 mg in HCV subjects are anticipated to be 3- to 30-fold below the exposures achieved in preclinical safety assessment toxicity studies and ancillary pharmacology studies. In the thorough QT study (MK-8408 PN007), a supratherapeutic dose of 600 mg RZR did not cause QTc prolongation and was generally well tolerated; there were no SAEs, deaths, or ECIs reported. This dose yielded a margin for maximum plasma concentration (C_{max}) of approximately 2.9-fold and AUC_{0-24} of approximately 2.3-fold relative to RZR steady state exposure at the 60-mg dose. Additionally, multiple doses of RZR were generally well tolerated after 100 mg once daily for 10 days in healthy subjects and 120 mg once daily for 5 days in HCV-infected subjects. The steady state exposures of RZR 180 mg in HCV subjects are anticipated to be similar to the clinical exposures achieved in the RZR thorough QT study, and expected to be well tolerated based on the preclinical and clinical exposures achieved to date in RZR program. The 180 mg dose was also chosen for this study because RZR exhibits less than dose-proportional PK over the 200 to 600 mg dose range; a dose greater than 180 mg is predicted to result in limited additional increase in RZR exposure. For detailed information, please refer to the RZR IB.

Taken together, the available data supported the evaluation of RZR in combination with MK-3682 as a highly efficacious 2-drug regimen, and this study PN041 (MK-3682 450 mg and RZR 180 mg) and the ongoing PN035 (MK-3682 450 mg and RZR 60 mg) will provide a robust dataset to further elucidate the dose response of RZR in combination with MK-3682 as a 2-drug regimen.

The single entity fit-for-purpose capsule formulation of RZR shows a moderate negative food effect, with a 50% decrease in C_{24hr} when co-administered with a high-fat meal. As such, in this study, subjects will be instructed to take study drugs on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Drugs should be taken with water, but without food. A drug-drug interaction study with MK-3682 and RZR (MK-3682 PN008) showed no clinically significant drug interactions, thus supporting the coadministration of these drugs without need for dose adjustment.

4.2.5 Rationale for Endpoints

4.2.5.1 Efficacy Endpoints

The primary measurement for efficacy in this study is the plasma HCV RNA level. Long-term suppression of HCV RNA, typically reported as SVR, has been associated with improved outcomes in subjects with chronic HCV infection as measured by biochemical and histological remission of liver disease. Most available data suggest that SVR following antiviral therapy reduces the risk of progression to cirrhosis and may prevent the development of severe liver complications as well as improve survival [37].

The primary evaluation of efficacy in this trial is based on SVR_{12}, the same endpoint used for all investigational and approved DAAs. Since a high degree of concordance has been observed between SVR_{12} and SVR_{24} [38], SVR_{12} is now being used as the primary endpoint for registration of DAAs. A secondary evaluation of efficacy is based on SVR_{24} and for this study this will be a secondary endpoint [39].

4.2.5.1.1 Measurement of HCV RNA

HCV-RNA levels in plasma will be measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each subject at various time points prior to, during, and after dosing, as indicated in the Trial Flow Chart (Section 6.0). Samples are collected and processed as per instructions provided by the manufacturer.

Results from the sample collected at the screening visit are used to determine eligibility. Samples collected at other time points, after Day 1, are used for efficacy analyses and to identify subjects who meet virologic failure criteria.

The nomenclature detailed in Table 5 will be used when describing HCV RNA levels:

Table 5 Nomenclature for Describing HCV RNA Levels

Abbreviation	Definition	HCV RNA Level
TND	Target not detected	HCV RNA not detected
TD(u)	Target detected but unquantifiable	HCV RNA <LLOQ
TD(q)	Target detected, quantifiable	HCV RNA ≥LLOQ

HCV = hepatitis C virus; LLOQ = lower limit of quantification; RNA = ribonucleic acid.

4.2.5.1.1.1 Definition of Efficacy Endpoints

Efficacy will be defined at different time points during the trial. Specific primary and secondary endpoints are:

- SVR_{12}: Subject has HCV RNA <LLOQ 12 weeks after the end of all study therapy.
- SVR_{24}: Subject has HCV RNA <LLOQ 24 weeks after the end of all study therapy.
- Virologic failure rate among subjects who do not discontinue the study for non-treatment-related reasons at FW12.

4.2.5.1.1.2 Definition of Virologic Failure: Non-Response, Rebound, Virologic Breakthrough and Relapse

Lack of efficacy at different time points in the trial will be categorized as:

- Non-response: Subject has HCV RNA detected at end of treatment without HCV RNA <LLOQ having been achieved while on treatment (note that breakthrough is distinguished below).
- Rebound: Subject has a rebound defined as >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.

- Virologic breakthrough: Subject has a confirmed HCV RNA ≥LLOQ (target detected, quantifiable [TD(q)]) after being <LLOQ previously while on treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.

- Relapse: Subject has a confirmed HCV RNA ≥LLOQ [TD(q)] following end of all study therapy, after becoming undetectable (target not detected [TND]) at end of treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.

4.2.5.1.2 Viral Resistance Measurements

Resistance-associated variants of the HCV can lead to failure of therapy. This is one of the most important considerations when treating with a DAA. To better understand and document the potential for RAVs to impact treatment with MK-3682 + RZR, blood samples for viral resistance assays will be collected at Baseline (Day 1) to determine pre-existing RAVs to MK-3682 and RZR. Next-generation sequencing will be performed with a 15% sensitivity threshold. Additional resistance testing on these samples may be performed. Blood samples for resistance testing are also collected during the follow-up period, as well as at the virologic failure confirmation visit (should this occur) for genotypic and investigational assays to assess emergence of resistance to MK-3682 and/or RZR following treatment initiation. Resistance-associated variants will be assessed for any subject who has detectable virus above 1000 IU/mL and has met a virologic failure criteria. Subjects who fail due to early discontinuation of study medication and continue in the trial may also have samples collected and tested for RAVs at each follow-up visit, if the virus is detectable and >1000 IU/mL.

4.2.5.2 Safety Endpoints

The safety and tolerability of the study regimen will be assessed by a clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examinations, 12-lead ECGs, and standard laboratory safety tests at appropriate time points as specified in the Trial Flow Chart (Section 6.0). Adverse events are graded and recorded according to Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.5.3 Pharmacokinetic Endpoints

The primary PK endpoints for MK-3682 (and metabolites) and RZR are trough plasma concentration (C_{trough}). PK samples will be collected from all subjects on each visit as described in the Trial Flow Chart (Section 6) and in Table 13 (Pharmacokinetic and Pharmacodynamic Sampling Time Points). These samples will be used to evaluate PK concentrations, and PK/AE relationships of MK–3682 (and metabolites) and RZR, as appropriate. The predose time points outlined were chosen in order to capture C_{trough} for all compounds. The frequency of C_{trough} collections will allow a thorough assessment of both subject drug concentrations and drug compliance, should a breakthrough occur. In addition, the postdose time points, in conjunction with the other samples, will be used for PK-safety and PK-efficacy modeling.

4.2.5.4 Pharmacodynamic Endpoints

As described in Section 7.1.3.2, a subgroup of the study population will be included in an intensive viral kinetic sub-study. The purpose of this sub-study is to determine whether early viral kinetics can aid in developing a PK/PD model that can predict combinations that may be efficacious with various treatment durations.

These subjects will have HCV RNA samples collected during Week 1 as described in the Trial Flow Chart (Section 6.0) and in Table 13 (Pharmacokinetic and Pharmacodynamic Sampling Time Points). In addition, PK samples will also be collected as described in Table 13. These samples will be used to evaluate the PK/PD relationships of MK-3682 (and metabolites) and RZR, as appropriate.

4.2.5.5 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

In addition to studying variation across the human genome, for example, IL28B genetic variants will specifically be investigated for understanding variation in clinical endpoints for example, but not limited to, SVR and other efficacy and safety measurements.

4.2.5.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

There remains a critical need for new HCV therapies. The treatment regimen combining an HCV NS5B NI (MK-3682), and an NS5A complex inhibitor (RZR), has the potential to provide efficacy across multiple GTs and across diverse patient populations, and improve treatment by eliminating the need for RBV and shortening the duration of therapy. The improved potency against RAVs observed with earlier generation NS5A inhibitors suggests that MK-3682 in combination with RZR may provide a stronger barrier to the development of resistance and increased activity in the setting of baseline resistance variants.

MK-3682

MK-3682 is a potent HCV NS5B NI with pangenotypic activity and a high barrier to resistance that, in combination with complementary HCV DAAs, has the potential to benefit an expanded spectrum of HCV-infected subjects, including those with currently difficult-to-treat GTs of HCV and individuals who have failed previous treatments. Among all the known DAA classes, NIs have displayed the broadest HCV genotypic coverage and the highest barrier to the development of resistance.

MK-3682 belongs to a class of uridine-based nucleotide analogs, e.g., SOF, that have been generally well tolerated. However, there have been postmarketing reports of symptomatic bradycardia, including one fatal cardiac arrest and cases requiring pacemaker insertion, in subjects taking the antiarrhythmic drug amiodarone together with either LDV/SOF or SOF in combination with another DAA.

The toxicity potential of MK-3682 has been well characterized in *in vitro* mitochondrial toxicity assays, a battery of *in vitro* and *in vivo* genetic toxicity studies, safety pharmacology studies, and 4-week, 3-month and 6-month repeat-dose oral toxicity studies in rats and monkeys. *In vitro* and *in vivo* preclinical data demonstrate that MK-3682 and its metabolite, M6, at the exposures observed in the clinic, have limited potential for class toxicities associated with nucleotides, including myopathy and mitochondrial toxicity. No observed adverse effect levels (NOAELs) in the rat and Cynomolgus monkey at 1000 mg/kg/day provide adequate margins of safety relative to anticipated human doses and support daily oral dosing of humans for up to 6 months in duration. In summary, the toxicity studies identified minimal differences between control and treated animals, all of which were not considered adverse. Preclinical studies identified the liver and potentially kidney as potential target organs. There was no evidence of cardiovascular toxicity in studies up to 3 months' duration, based on histopathology in the rat and monkey and echocardiography, electrocardiography, and serum biomarker evaluations in the monkey. Overall, the preclinical toxicity profile of MK-3682 via the oral route of administration supports the continuation of clinical trials.

To date, MK-3682 has been generally well-tolerated in healthy subjects and HCV-infected subjects in several Phase 1 clinical studies at single doses up to 900 mg, multiple doses up to

750 mg per day for 10 days, and in Phase 2a trials of 300 mg or 450 mg once daily for up to 24 weeks. Review of the safety data has revealed no clinically significant abnormalities in routine physical examinations including vital signs. There have been no dose-related or other patterns observed in the clinical, ECG, or laboratory data. In the clinical studies proposed, available safety data (clinical and laboratory AEs, vital signs, laboratory safety tests, and ECGs) will be carefully monitored.

Phase 2 studies have demonstrated that a regimen of MK-3682 (450 mg)/GZR/RZR is highly effective in GT1, 2, and 3-infected subjects. Overall, MK-3682, as a component of a combination DAA regimen, has the potential to substantially improve HCV treatment outcomes, benefiting many HCV-infected individuals.

RZR

RZR is a potent HCV NS5A complex inhibitor with pangenotypic activity that has the potential to benefit individuals requiring treatment of HCV infection, even if the individual is infected with currently difficult-to-treat GTs. The improved potency of RZR against RAVs observed with earlier generation NS5A inhibitors suggests that RZR will have improved efficacy in individuals who have experienced treatment failures with other anti-HCV regimens and/or have NS5A RAVs at baseline.

RZR has favorable safety findings in safety assessment toxicity studies and ancillary pharmacology studies, supporting the continued evaluation of RZR in clinical trials in adults. The 2-week, 3-month, 6-month, and 9-month rat and dog toxicity studies provide substantial preclinical safety margins for doses proposed to be administered in future clinical trials. RZR has been given to approximately 217 subjects and subjects in 8 RZR Phase 1 trials and in over 800 subjects in ongoing Phase 2a trials (RZR in combination with MK-3682 and GZR in HCV GT1-, GT2-, and GT3-infected subjects). RZR has been administered at doses up to 600 mg/day, 100 mg given daily for 10 days, and 60 mg once daily for up to 24 weeks. No SAEs have been reported in any individual receiving RZR. There were no consistent treatment-related changes in labs, vital signs, or ECG safety parameter values. Adverse events in subjects receiving RZR monotherapy have been mild to moderate in intensity and transient in duration. The totality of the safety data indicates that RZR is well-tolerated.

Definitive embryo-fetal developmental toxicity studies conducted in concordance with the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use M3 (R2) guidance have been completed in rats and rabbits for MK-3682 and RZR. While data support the inclusion of women of childbearing potential in clinical trials with MK-3682 and RZR, inclusion of women of childbearing potential should be in accordance with the study protocol and applicable regulatory guidance.

Based on the preclinical data and the clinical experience to date in healthy subjects and HCV-infected subjects, the risk/benefit assessment is favorable for proceeding with the proposed clinical study with the 2-drug combination of MK-3682 + RZR.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with chronic HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection who are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. be ≥18 years of age on day of signing informed consent
2. have HCV RNA (≥10,000 IU/mL in peripheral blood) at the time of screening
3. have documented chronic HCV GT1, GT2, GT3, GT4, GT5, or GT6 (with no evidence of non-typeable or mixed GT) infection as follows:
    a. positive for anti-HCV antibody, HCV RNA, or HCV GT1, GT2, GT3, GT4, GT5, or GT6 at least 6 months before Day 1, **or**
    b. positive for anti-HCV antibody or HCV RNA with a liver biopsy consistent with chronic HCV infection (such as the presence of fibrosis) before Day 1
4. have liver disease staging assessment as follows:
    a. <u>Absence of cirrhosis (F0 to F3)</u> defined as any one of the following:
        i. a liver biopsy performed within 24 months of Day 1 of this study showing absence of cirrhosis
        ii. Fibroscan® performed within 12 months of Day 1 of this study with a result of ≤12.5 kPa, **or**
        iii. a Fibrosure® (Fibrotest®) performed during screening with a score of ≤0.48 **and** an aspartate aminotransferase (AST) to platelet ratio index (APRI) of ≤1
    b. <u>Compensated cirrhosis (F4)</u> defined as any one of the following:
        i. a liver biopsy performed prior to Day 1 of this study showing cirrhosis
        ii. Fibroscan® performed within 12 months of Day 1 of this study showing cirrhosis with result >12.5 kPa, **or**
        iii. a Fibrosure® (Fibrotest®) performed during screening with a score of >0.75 **and** an APRI of >2

    APRI formula: AST ÷ lab ULN for AST × 100 ÷ (platelet count ÷ 100). APRI calculation to be provided by the testing laboratory.

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®.

5. have an HCV treatment status that is one of the following:
   a. HCV treatment naïve (defined as no prior exposure to any IFN-containing regimen, RBV, or other approved or experimental HCV-specific DAA agent).
   b. HCV treatment experienced (defined as prior virologic failure after treatment with an IFN-containing regimen, with or without RBV, or intolerance to an IFN-containing regimen). Subjects cannot have previously received treatment with HCV-specific DAA agent.
6. meet one of the following categories:
   a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
   b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.
   c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner beginning at least 2 weeks prior to administration of the initial dose of study drug, and for **6 months after taking the last dose** of study drug (or longer if dictated by local regulations) by complying with 1 of the following: (1) practice abstinence† from heterosexual activity OR (2) use (or have their partner use) **2** forms of acceptable contraception during heterosexual activity. Acceptable methods of contraception are as follows‡:
      - intrauterine device (with or without local hormone release)
      - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
      - cervical cap with spermicide (nulliparous women only)
      - contraceptive sponge (nulliparous women only)
      - male condom with spermicide or female condom with spermicide (cannot be used together)
      - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

If male, subjects must agree to use a condom with spermicide or abstain from sexual intercourse during the trial until **6 months after taking the last dose** of study drug (or longer if dictated by local regulations).

Spermicides alone are not an acceptable method of contraception.

Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this trial.

If there is any question that a subject will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the trial.

NOTE: Subjects whose study medication regimen includes only MK-3682 + RZR (and are not treated at any time with RBV) should avoid becoming pregnant or impregnating a partner for at least **14 days after taking the last dose** of study drug. Acceptable methods of contraception for these subjects during this time include:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

7. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent. The subject may also provide consent for FBR. However, the subject may participate in the main trial without participating in FBR.

For HIV co-infected subjects, these additional 2 criteria must also be met:

8. have HIV-1/HIV-2 infection documented at any time prior to study entry (Day 1) by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA VL.
9. meet 1 of the following criteria:
    a. not currently on antiretroviral therapy (ART) and has no plans to initiate ART treatment while participating in this study, must have CD4+ T-cell count >500 cells/mm^3 at time of screening, or
    b. have well controlled HIV on ART, defined as the following:
        i. must have CD4+ T-cell count >200 cells/mm^3 at time of screening
        ii. must have achieved and maintained virologic suppression (defined as confirmed HIV RNA level <LLOQ of available assay) for at least 8 weeks prior to screening
        iii. must have been on a stable regimen (without changes in drugs or dose modification) for at least 4 weeks prior to study entry (Day 1)

            The combination ART regimen must not contain any antiretroviral medications other than: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine or tenofovir.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. is under the age of legal consent, is mentally or legally incapacitated, has significant emotional problems at the time of pre-study screening visit or expected during the conduct of the study, or has a history of a clinically significant psychiatric disorder which, in the opinion of the investigator, would interfere with the study procedures.
2. has evidence of decompensated liver disease manifested by the presence of or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver disease.
3. is cirrhotic AND has a Child-Turcotte-Pugh score >6, corresponding to a Child Class B or C

    NOTE: To calculate the Child-Turcotte-Pugh score and classification, refer to the following website: http://www.mdcalc.com/child-pugh-score-cirrhosis-mortality/.
4. is hepatitis B surface antigen (HBsAg) positive at screening.

    NOTE: Subjects who are HBsAg negative at screening, but who are hepatitis B core antibody (anti-HBc) positive at screening may be included. For all anti-HBc positive subjects, hepatitis B virus (HBV) deoxyribonucleic acid (DNA) will be assessed at

screening, and both HBV DNA and HBsAg will be monitored during the trial. Additional details can be found in Section 7.1.3.5 – HBV Evaluation and Section 7.2.3.2 – Events of Clinical Interest.

5. is coinfected with HIV AND has a history of opportunistic infection in the preceding 6 months prior to screening.

   NOTE: A list of these events may be found in Appendix B of the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

6. has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer or carcinoma *in situ*; or is under evaluation for other active or suspected malignancy.

7. has cirrhosis AND liver imaging within 6 months of Day 1 showing evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC.

   NOTE: If liver imaging within 6 months prior to Day 1 is not available, imaging is required during screening.

8. is taking or plans to take any of the prohibited medications listed in the protocol (Section 5.5) or is taking herbal supplements, including but not limited to St. John's wort (*Hypericum perforatum*), from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.

9. is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent and is not willing to refrain from participating in another such study during the course of this study through 24 weeks after the study treatment period (FW 24).

10. is a female subject who is pregnant or breastfeeding, or expecting to conceive or donate eggs from Day 1 through 6 months after the last dose of study drug or longer if dictated by local regulations, OR a male subject who is expecting to donate sperm from Day 1 through 6 months after the last dose of study drug or longer if dictated by local regulations.

    NOTE: Female subjects whose study medication regimen includes only MK-3682 + RZR (and are not treated at any time with RBV) should avoid conceiving or donating eggs for at least 14 days after taking the last dose of study drug. Male subjects whose study medication regimen includes only MK-3682 + RZR (and are not treated at any time with RBV) should avoid impregnating a partner or donating sperm for at least 14 days after taking the last dose of study drug.

11. is a male whose female partner(s) is/are pregnant (this is a contraindication for RBV use).

12. has any of the following conditions:

a. Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.

b. Poor venous access that precludes routine peripheral blood sampling required for this trial.

c. Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).

d. has clinically relevant drug or alcohol abuse within 12 months of screening that may interfere with subject treatment, assessment, or compliance with the protocol.

e. Any clinically significant cardiac abnormalities/dysfunction that may interfere with subject treatment, assessment, or compliance with the protocol, including but not limited to: unstable angina, unstable congestive heart failure, unstable arrhythmia; subjects currently under evaluation for a potentially clinically significant cardiac abnormality/dysfunction are also excluded.

f. Any major medical condition, clinically-significant illness (other than HCV), pre-study laboratory or ECG abnormality, or history of any illness, which, in the opinion of the investigator, might interfere with subject treatment, assessment, compliance with the protocol, or confound the results of the study or pose additional risk in administering the study drug to the subject.

g. History of a medical/surgical condition that resulted in hospitalization within the 3 months prior to enrollment, other than for minor elective procedures.

NOTE: Elective procedures will be permitted following 14 days after taking the last dose of study drug.

h. Medical/surgical conditions that may result in a need for hospitalization during the period of the study.

i. Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, tumor necrosis factor (TNF) antagonists, or other immunosuppressant drugs during the course of the trial through FW24.

j. Life-threatening SAE during the screening period.

k. Evidence of history of chronic hepatitis not caused by HCV, including but not limited to drug-induced hepatitis, hemochromatosis, Wilson's disease, α1-antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis (See Exclusion Criterion #4 regarding evidence of history of Hepatitis B).

NOTE: Subjects with history of acute non-HCV-related hepatitis, which resolved >6 months before study entry, can be enrolled.

13. has exclusionary laboratory values at the screening visit as listed in Table 6.

NOTE: If any of the laboratory exclusion criteria in Table 6 are met, the site may have the abnormal value retested 1 time.

Table 6 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Values
Creatinine Clearance (estimated glomerular filtration rate, eGFR)[1]	<50 mL/min/1.73 m^2
Hemoglobin	<10 g/dL
Platelets	<50 × 10^3/µL
Serum Albumin	<3.0 g/dL
International normalized ratio (INR)	>1.7 unless subject has a stable INR on an anticoagulant regimen
ALT	>10× ULN
AST	>10× ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtratrion rate; INR = international normalized ratio; ULN = upper limit of normal. [1] Creatinine clearance will be evaluated as an eGFR based on the modification of diet in renal disease (MDRD) equation: eGFR (mL/min/1.73 m^2) = 175 × (Scr, std)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if black) Scr, std: serum creatinine measured with a standardized assay.	

14. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 7.

Table 7 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
MK-3682 (150-mg tablets)	450 mg	Daily (3 tablets once daily)	Oral	12 weeks	Experimental
RZR (60-mg capsules)	180 mg	Daily (3 capsules once daily)	Oral		Experimental
[a] If the efficacy criteria for stopping enrollment/treatment allocation are met for that particular GT, the treatment regimen with MK-3682 + RZR for subjects with a particular GT still receiving treatment will be extended to a total duration of 16 weeks and RBV will be added to the regimen (see Table 8 and Section 5.11.4).					

Rescue medication to be used in this trial if efficacy criteria for stopping enrollment/treatment allocation are met for a particular GT (see Section 5.11.4) is outlined below in Table 8. Ribavirin should be dosed according to the approved local prescribing information.

Table 8 Rescue Medication

Drug	Weight	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-3682 (150-mg tablets)	NA	450 mg	Daily (3 tablets once daily)	Oral	Total of 16 weeks	Rescue Medication
RZR (60-mg capsules)	NA	180 mg	Daily (3 capsules once daily)	Oral	Total of 16 weeks	Rescue Medication
Ribavirin only if treatment duration is extended	Per approved local prescribing information			Oral	Maximum of 16 weeks	Rescue Medication

All clinical supplies indicated above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

The first dose of trial treatment will be administered at the trial site at Visit 2 (Day 1). The doses to be taken at other visits at which a pre-dose PK sample is to be collected will also be administered at the trial site. See Section 5.2.2 for specific dosing instructions. Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification

Dose modification of MK-3682 or RZR is not permitted. See Section 5.2.2 for instructions if for any reason MK-3682 or RZR needs to be interrupted. For any other dose modifications that occur, consult the Sponsor Protocol team.

Ribavirin

Dose modification of RBV is permitted per the approved local prescribing information.

5.2.2 Timing of Dose Administration

MK-3682 and RZR

All doses of MK-3682 and RZR should be taken on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Study medications should be taken with water but without food. In addition, subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2) and for all other visits at which a pre-dose PK sample is to be collected. For study visits after Visit 2, if there are cases in which a morning visit is not feasible and a subject is seen in the afternoon, the subject should take their study medication in the morning, after an overnight fast, as per their regular schedule and PK samples will still be collected during these visits.

If a subject misses a dose of MK-3682 or RZR and it is less than 8 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. Subjects should not double the next dose in order to compensate for what has been missed.

If a subject misses a dose of MK-3682 or RZR and it is greater than 8 hours before the next dose, the missed dose should be taken at least 2 hours after last meal and 1 hour before next meal and the normal dosing schedule resumed.

If for any reason MK-3682 or RZR needs to be interrupted, the entire regimen should be interrupted and can be interrupted for up to 3 days. If the interruption lasts for more than 3 days, consult the Sponsor Protocol team.

Ribavirin

Dosing of RBV should follow the approved local prescribing information.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

In this nonrandomized, open-label trial, subjects will be assigned to receive MK-3682 + RZR. Treatment allocation will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Ribavirin will be locally sourced and dispensed by the site if the treatment regimen is extended.

5.4 Stratification

Subjects will be stratified by GT according to the following plan. After the first 50 subjects (of any GT) are allocated to treatment, allocation will pause to assess general safety and tolerability. If general safety and tolerability is assessed to be acceptable, the subsequent 200 subjects will be allocated to treatment with an overall allocation target based on GT (GT1, GT2, GT3, GT4, GT5, or GT6). The first 50 subjects will be included in the overall treatment allocation target of the trial, and counted towards the GT and fibrosis stage allocation targets (see Section 2.1).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Prohibited Medication

It is important for investigators to review each medication (prescription and non-prescription) the subject is taking before starting the study and at each study visit.

- All concomitant medications/therapies should be reviewed and data collected through 2 weeks after the study treatment period. Subjects should be questioned about any new drugs/vaccines they are taking/have taken or changes to any previously reported drugs/vaccines.
    - Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- Non-study HCV medications/therapies, including interferon, are prohibited through FW24. Any use should be reported throughout the subject's participation in the trial.

Listed below (Table 9) are specific restrictions for concomitant therapy during the course of the trial.

The following medications/therapies are not permitted from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.

Table 9 List of Prohibited Medications

Category	Examples
Known hepatotoxic drugs, including but not limited to the following:	etifoxine, isoniazid, nitrofurantoin
Herbal supplements:	All herbal supplements are prohibited (e.g., silymarin [milk thistle] and St. John's wort)
Antiarrhythmic agents, including but not limited to the following:	amiodarone, quinidine, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone
Strong inhibitors of CYP3A, including but not limited to the following:	clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone
Strong and moderate CYP3A inducers, including but not limited to the following:	Anti-infectives: nafcillin, rifampin Anticonvulsants: carbamazepine, phenytoin, phenobarbital Endothelin antagonists: bosentan Wakefulness-Promoting Agents: modafinil Herbal Products: St. John's wort
Gastric acid modifiers:	H2 blockers Proton-pump inhibitors *Note: antacids, such as calcium carbonate or aluminum hydroxide-based product, will be allowed during the study, but it is recommended they be taken either 4 hours before or after dosing of MK-3682 and RZR (see Allowed Medication below)*
HIV medications (note that not all prohibited HIV medications are listed):	efavirenz etravirine nevirapine ritonavir all boosted and unboosted HIV protease inhibitors *Note: see Allowed Medication below for list of permitted HIV medications*
HMG-CoA reductase inhibitors (statins):	rosuvastatin greater than a daily dose of 10 mg (see Allowed Medications, below) atorvastatin, fluvastatin, lovastatin, or simvastatin greater than a daily dose of 20 mg (see Allowed Medications, below).
CYP = Cytochrome P450; HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.	

Allowed Medications

The following concomitant medications (Table 10) are allowed in this study.

Table 10 List of Allowed Medications

Antihypertensives:	ACE inhibitors or ARBs: enalapril, captopril, lisinopril, ramipril, valsartan, losartan, telmisartan Beta blockers: atenolol, metoprolol, propranolol *(NOTE: for other beta blockers, please consult with the Sponsor)* Calcium-channel blockers: amlodipine, diltiazem, verapamil *(NOTE: for other calcium-channel blockers, please consult with the Sponsor)* hydralazine, clonidine, minoxidil, isosorbide nitrates
Anemia:	erythropoietin
Anti-coagulants:	warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol
Diuretics:	HCTZ, furosemide, spironolactone, triamterene
Hypoglycemic agents:	insulin, sitagliptin, glipizide, metformin
Contraceptives:	oral contraceptive pills, progesterone injects, intrauterine devices
Antidepressants/anxiolytics:	citalopram, paroxetine, duloxetine, escitalopram, fluoxetine, bupropion, trazodone, diazepam, clonazepam, temazepam, lorazepam
Acid reflux:	Antacids: stomach acid neutralizers, such as calcium carbonate or aluminum hydroxide-based products, are permitted, but it is recommended that they be taken either 4 hours before or after dosing of MK-3682 and RZR
HIV medications:	abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, tenofovir
HMG-CoA reductase inhibitors (statins):	pravastatin and pitavastatin: may be coadministered without dose adjustment rosuvastatin: use the lowest possible effective dose of rosuvastatin, but do not exceed a daily dose of 10 mg atorvastatin, simvastatin, fluvastatin, lovastatin: use the lowest possible effective dose of atorvastatin, but do not exceed a daily dose of 20 mg
Opioid agonist therapy:	Subjects on stable doses of methadone or buprenorphine/naloxone may be enrolled in this study, if not excluded per Exclusion Criteria in Section 5.1.3.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HCTZ = hydrochlorothiazide; HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.	

In general, P-glycoprotein substrates with narrow therapeutic ranges (e.g., digoxin and colchicine) are not prohibited, but their levels have the potential to be increased. Therefore, subjects taking these medications should be monitored closely.

Given that the lists above are not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or consult with the Sponsor.

5.6 Rescue Medications & Supportive Care

The treatment regimen with MK-3682 + RZR for subjects with a particular GT will be extended to 16 weeks' duration and RBV will be added, if the efficacy criteria for stopping enrollment/treatment allocation are met for that particular GT.

5.7 Diet/Activity/Other Considerations

MK-3682 and RZR should be taken with water and without food (on an empty stomach after an overnight fast and at least 1 hour before the morning meal). For subjects whose treatment regimen is modified to include RBV, dosing of RBV should follow the approved local prescribing information.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the trial will still continue to participate in the trial as specified in Section 6.0, Trial Flow Chart and Section 7.1.5.6, Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.

Table 11 provides reasons why a subject must be discontinued from treatment but should continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 11 Discontinuation Scenarios

Reason for Discontinuation Scenario	***Action***
The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinue from Treatment and Trial
Subject meets criteria for HCV virologic breakthrough or rebound (see Section 4.2.3.1.1.2)	Discontinue from Treatment (should continue to monitor in the trial)
Subject becomes pregnant during the trial.	Discontinue from Treatment (should continue to monitor in the trial)
A physician investigator feels it is in the best interest of the subject to discontinue.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's ALT or AST increases to >500 IU/L and is confirmed with repeat test within one week.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's ALT or AST increases to >3x the nadir value, is >3x ULN (confirmed with repeat test within one week), and there is a simultaneous increase in total bilirubin > 2x ULN and/or INR is increased from the baseline value and is >1.5 (unless the subject is on anticoagulation).	Discontinue from Treatment (should continue to monitor in the trial)
The subject's ALT or AST increases to >3x nadir, is >3x ULN (confirmed with repeat test within one week), and is temporally associated with signs or symptoms of liver inflammation that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to study therapy.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's serum creatinine increases to Grade 3 or higher (>1.8× upper limit of normal), confirmed with repeat test within one week.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's creatinine clearance (eGFR) decreases to <50 mL/min/1.73 m^2, confirmed with repeat test within one week. Creatinine clearance will be evaluated as an estimated GFR (eGFR), based on the modification of diet in renal disease (MDRD) equation: eGFR (mL/min/1.73 m^2) = 175 × (Scr, std)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if black) Scr, std: serum creatinine measured with a standardized assay	Discontinue from Treatment (should continue to monitor in the trial)
The subject has a Grade 4 laboratory AE, or a life-threatening clinical AE, or an AE that results in or prolongs an existing in-subject hospitalization, that is assessed as study drug-related	Discontinue from Treatment (should continue to monitor in the trial)
SAE assessed by the physician investigator as possibly or probably related to study medication. Investigator may continue the subject in the trial, if it is deemed to be in the best interest of the subject to stay on the study treatment after consultation with Sponsor.	**May** Discontinue from Treatment (should continue to monitor in the trial)
Failure to comply with the dosing, evaluations, or other requirements of the trial.	**May** Discontinue from Treatment (should continue to monitor in the trial)

Note: Clinical management of HIV-1 virologic failure will be handled by site investigators according to current HIV treatment guidelines and local standard of care. Subjects with HIV virologic failure may continue in the trial unless treatment with a prohibited concomitant medication (Section 5.5) is required to construct a new HIV treatment regimen.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.6 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate upon consultation with the SPONSOR.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or legal representative (such as parent or legal representative) withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from treatment or withdraws from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

5.11.1 Criteria for Assessing Safety in the First 50 Subjects

The following criteria apply to stopping further allocation after the first 50 subjects have commenced treatment, and not continuing allocation to reach the overall target of n=250.

These criteria will be assessed after the last of the first 50 subjects reaches TW4, as this allows for steady state of drug to be achieved for ≥2 weeks.

If >3 out of the first 50 subjects receiving MK-3682 + RZR experience any of the following, study therapy will be discontinued in all subjects and no additional subjects will be enrolled or allocated to treatment.

- The subject has a Grade 4 laboratory abnormality, or a life-threatening clinical AE, or an AE that results in or prolongs an existing hospitalization, or death, that is assessed to be study drug related.
- The subject's ALT or AST increases to >500 IU/L, is assessed to be study drug related, and is not associated with virologic failure.
- The subject's serum creatinine increases to Grade 3 or higher (>1.8 × ULN), confirmed with repeat test within 1 week, that is assessed to be study drug related.
- The subject's creatinine clearance (eGFR) decreases to <50 mL/min/1.73 m^2, confirmed with repeat test within 1 week, that is assessed to be study drug related.

  Note: Creatinine clearance will be evaluated as an eGFR based on the modification of diet in renal disease (MDRD) equation:

  $eGFR\ (mL/min/1.73\ m^2) = 175 \times (Scr, std)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black)$

  Scr, std: serum creatinine measured with a standardized assay

5.11.2 Safety Criteria for Stopping Enrollment/Allocation At Any Time During the Trial

If >12 subjects receiving MK-3682 and RZR, at any time during the trial, experience any 1 of the following, the trial will terminate.

- The subject has a Grade 4 laboratory abnormality, or a life-threatening clinical AE, or an AE that results in or prolongs an existing hospitalization, or death, that is assessed to be study drug related.
- The subject's ALT or AST increases to >500 IU/L, is assessed to be study drug related, and is not associated with virologic failure.
- The subject's serum creatinine increases to Grade 3 or higher (>1.8 × ULN), confirmed with repeat test within 1 week, that is assessed to be study drug related.
- The subject's creatinine clearance (eGFR) decreases to <50 mL/min/1.73 m^2, confirmed with repeat test within 1 week, that is assessed to be study drug related.

  Note: Creatinine clearance will be evaluated as an eGFR based on the modification of diet in renal disease (MDRD) equation:

  $eGFR\ (mL/min/1.73\ m^2) = 175 \times (Scr, std)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black)$

  Scr, std: serum creatinine measured with a standardized assay

5.11.3 Safety Criteria for Pausing Enrollment/Allocation

If ≥3 subjects receiving MK-3682 and RZR experience any of the following during the study, treatment allocation will be paused:

- The subject has a Grade 4 laboratory abnormality, or a life-threatening clinical AE, or an AE that results in or prolongs an existing hospitalization, or death, that is assessed to be study drug related.

Subjects who are tolerating treatment may continue to receive study therapy, but no additional subjects will be allocated to treatment until the Sponsor has reviewed all safety data on subjects.

5.11.4 Efficacy Criteria for Stopping Enrollment/Allocation

The efficacy criteria for stopping enrollment/treatment allocation are:

1. A total of ≥3 out of the first 10 subjects in the per-protocol (PP) population (see Section 8.5.1 for definition) for each GT (GT1-6) receiving 12 weeks of therapy experience virologic failure (non-response, rebound, breakthrough, or relapse) by FW4, or
2. >5 subjects in the PP population for GT1-4, and >3 subjects in the PP population for GT5-6, experience virologic failure at any point in the trial.

If either of these criteria is met, then no additional subjects of that particular GT would be allocated to treatment in the trial. Additionally, the Sponsor will review the results, and if the majority of failures are due to relapses (i.e., >50%), the treatment regimen will be modified for all subjects of that GT still on treatment. If the treatment regimen is modified, the duration will be extended to 16 weeks and RBV will be added to the regimen (investigators will review considerations and contraindications to RBV with subjects impacted).

Criteria for HIV-infected Subjects

If a total of ≥2 HIV-infected subjects across all arms experience confirmed loss of HIV-1 virologic suppression at any time, then no additional HIV co-infected subjects will be enrolled. Loss of virologic suppression is defined as HIV-1 RNA ≥200 copies/mL, confirmed on 2 consecutive tests at least 2 weeks apart in subjects compliant with their HIV ARV therapies. Remaining co-infected subjects who are already on trial treatment will continue their assigned HCV treatment regimen while their HIV regimen is being reassessed.

6.0 TRIAL FLOW CHART

Trial Period		Treatment Period													Follow-up Period						Unscheduled	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Intensive PK/PD group:	Screening	Day 1[1]	Day 2	Day 3	Day 5	Day 7	TW2	TW4	TW6	TW8	TW10	TW12	TW14[2]	TW16[2]	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Failure Confirmation Viral (HCV or HIV)	Early Discontinuation Visit
Main Study Group			n/a	n/a	n/a																	
Visit Window	-45d	n/a	n/a	+2d	-1d to +2d	-2d to +2d	-7 to +7 days					-7 to +14 days			-2 to +2 weeks						n/a	n/a
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X																					
Subject Identification Card	X	X																				
Medical History	X																					
Prior & Concomitant Medication Review[3]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Allocation		X																				
Study Medication Diary: Distribute and/or and Review Instructions		X	X	X	X	X	X	X	X	X	X	X	X	X								X
Reconcile Study Medication/Assess Compliance			X	X	X	X	X	X	X	X	X	X	X	X								
Telephone Contact																		X	X			
Clinical Procedures/Assessments																						
Comprehensive Physical Examination[4]	X																					
Focused PE[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Height		X																				
Weight		X																				
12-Lead Electrocardiogram	X	X		X[5]		X[5]	X	X		X		X			X		X					
Vital Signs (heart rate, blood pressure, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X
Subject Confirmation of Birth Control	X	X					X	X	X	X	X	X	X	X	X	X[6]	X[6]			X[6]	X[7]	X[7]
Review Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period		Treatment Period													Follow-up Period						Unscheduled	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Intensive PK/PD group:	Screening	Day 1[1]	Day 2	Day 3	Day 5	Day 7	TW2	TW4	TW6	TW8	TW10	TW12	TW14[2]	TW16[2]	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Failure Confirmation (HCV or HIV)	Early Discontinuation Visit
Main Study Group			n/a	n/a	n/a																	
Visit Window	-45d	n/a	n/a	+2d	-1d to +2d	-2d to +2d	-7 to +7 days					-7 to +14 days			-2 to +2 weeks						n/a	n/a
Laboratory Safety Evaluations																						
Chemistry & Hematology	X	X				X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Urinalysis	X	X				X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Coagulation	X	X				X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Urine Pregnancy Test (females of child bearing potential only)[9]	X	X					X	X	X	X	X	X	X	X	X	X[6]	X[6]			X[6]	X[7]	X[7]
HBV Evaluations[10]																						
HBsAg	X	X						X		X		X		X	X		X			X		
Anti-HBc	X																					
Anti-HBs	X																					
HBV DNA	X	X						X		X		X		X	X		X			X		
Pharmacokinetics[11]																						
MK-3682 and Metabolites		X		X[11]		X[11]	X	X	X	X		X		X							X[12]	X[12]
RZR		X		X[11]		X[11]	X	X	X	X		X		X							X[12]	X[12]
Meal Information for PK		X		X[11]		X[11]	X	X	X	X		X		X							X[12]	X[12]
HCV Evaluations																						
HCV RNA[13]	X	X	X[11]	X[11]	X[11]	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X[14]
HCV Genotype Determination	X																					
Liver Imaging[15]	X																					
Plasma for HCV Viral Resistance[16]		X													X	X	X			X	X	X[14]
Blood for genetic analysis[17]		X																				
HIV Evaluations[18]																						
HIV Serology	X																					
HIV RNA	X	X				X	X	X	X	X	X	X	X	X	X	X	X			X		X
Plasma for HIV Viral Resistance																					X[19]	
CD4+ T-cell Count	X	X				X	X	X	X	X	X	X	X	X	X	X	X			X		X
Drug Administration[20]																						
Dispense MK-3682 (open-label)		X						X		X		X										
Dispense RZR (open-label)		X						X		X		X										
Only if treatment duration is extended, dispense RBV (open-label)		X						X		X		X										

AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; d = day; DNA = deoxyribonucleic acid; FBR = future biomedical research; FU = Follow-up; FW = Follow-up Week; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRB/IEC = Institutional Review Board/Independent Ethics Committee; n/a = not applicable; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; RBV = ribavirin; RNA = ribonucleic acid; RZR = ruzasvir; TW = Treatment Week

[1] Procedures on Visit 2, Day 1 should be performed prior to the first dose unless specified otherwise.

[2] **TW14 and TW16 will only occur for those subjects whose treatment duration may be extended. PK sample scheme for these subjects remain the same with the addition of TW16 time point.**

[3] Non-study HCV medications/therapies are prohibited through FW24. Any use should be reported throughout the subject's participation in the trial.

[4] A comprehensive PE will be done at screening. For all other visits, a focused PE will be conducted when clinically indicated.

[5] Additional ECGs will be collected on subjects in the Intensive PK/PD group at Day 3 and Day 7.

[6] This procedure only applies to female subjects of child bearing potential whose treatment regimen is modified to include RBV.

[7] This procedure is performed only when the visit occurs prior to FW4. For female subjects of child bearing potential whose treatment regimen is modified to include RBV, urine pregnancy test and birth control confirmation should be performed when the visit occurs anytime through FW24.

[8] All AEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure. From the time of treatment allocation through 14 days following cessation of treatment, all AEs must be reported by the investigator. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

[9] For subjects whose treatment regimen is modified to include RBV, when study visits are spaced more than 1 month apart in the follow-up period, urine pregnancy test kits will be dispensed to female subjects of childbearing potential so that monthly pregnancy testing can continue for 6 months after dosing (or longer if dictated by local regulations). The test results must be provided to the investigator and/or site personnel. Subjects should be instructed to contact the investigator and/or site personnel immediately if the result of the self-pregnancy test is positive. A serum pregnancy test will be performed whenever a urine pregnancy test yields a positive result.

[10] HBsAg, anti-HBc, and anti-HBs will be assessed at screening in all subjects. For all anti-HBc positive subjects, HBV DNA will also be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial.

[11] PK samples will be collected as described in Section 7.1.3.2. Only subjects in the Intensive PK/PD group will have PK samples collected on Day 3, and post dose on Day 7. These subjects will also have additional HCV RNA samples collected postdose on Day 1-2, Day 3, and Day 5.

[12] PK samples and meal information for PK are to be collected at HCV/HIV viral confirmation or early discontinuation visits that occur only during the study treatment period.

[13] Leftover main study plasma will be stored at the end of the study for FBR if the subject consents to FBR.

[14] If a subject is a confirmed viral failure during therapy (i.e., breakthrough), then sample collection for HCV RNA and Viral Resistance/Biomarker is not needed for the early discontinuation visit.

[15] For cirrhotic subjects only, imaging is required within 6 months of randomization to evaluate for hepatocellular carcinoma. If liver imaging within 6 months prior to Day 1 is not available, imaging is required during screening.

[16] Blood samples will be collected for HCV viral resistance testing at Day1, virologic failure confirmation visits, and all follow-up visits after virologic failure confirmation or after early study medication discontinuation if the subject has quantifiable HCV RNA and is not the result of a virologic failure during therapy (i.e., rebound, breakthrough). Leftover main study plasma will be stored at the end of the study for FBR if the subject consents to FBR.

[17] This sample will be drawn for IL28B genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to IL28B. Leftover extracted DNA will be stored for FBR if the subject signs the FBR consent.

[18] HIV serology (HIV-1 and HIV-2) will be performed at screening for all subjects. HIV RNA and CD4+ T cell count at screening will only be processed for those subjects who have positive HIV serology. HIV evaluations will only be performed at Day 1 and subsequent visits as indicated in subjects that are HIV co-infected.

[19] In subjects who are HIV co-infected, blood samples will be collected for HIV viral resistance at the time of HIV RNA failure confirmation visit.

[20] Study medication will be dispensed at Day 1 and then every 4 weeks thereafter: Week 4 and Week 8. If the treatment regimen is extended, MK-3682 + RZR also will be dispensed at Week 12. RBV should be locally sourced and dispensed by the site if the treatment regimen is extended. Note that the duration of treatment with MK-3682 + RZR for subjects with a particular GT may be extended to 16 weeks' duration and RBV added to the regimen if the efficacy criteria for stopping enrollment/treatment allocation are met for that particular GT. For example, if efficacy criteria for stopping enrollment/treatment allocation are met for GT1-infected subjects at TW8, GT1-infected subjects already on treatment will receive MK-3682 + RZR for an additional 8 weeks (i.e., 16 weeks' total duration) + RBV for 8 weeks.

All doses of MK-3682 and RZR should be taken on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Study medications should be taken with water but without food. In addition, subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2) and for all other visits at which a pre-dose PK sample is to be collected. MK-3682 and RZR (open-label) will be provided by the Sponsor to cover a maximum of 32 days of dosing (4 weeks + 4 days). An unscheduled visit must occur to get additional drug if the subject will run out of study drug prior to the next scheduled visit. If dosing is missed or interrupted (see Section 5.2.2), the assigned study therapy regimen should still be completed.

For subjects whose treatment regimen is modified to include RBV, RBV is to be dosed according to the approved local prescribing information.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject through 2 weeks after the study treatment period. The investigator or qualified designee will discuss with the subject the necessity of not taking any concomitant medications or herbal preparations with known suspected hepatotoxic potential. If medications with potential hepatotoxicity cannot be discontinued in a subject, the investigator or qualified designee must discuss the inclusion of the subject with the Sponsor's clinical director who must approve the use of the medication prior to inclusion of the subject in the trial. To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential. Non-study HCV medications/therapies are prohibited through FW24. Any use should be reported throughout the subject's participation in the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication)

The investigator/study coordinator will give the subject a Study Medication Diary (SMD) to be completed during the study period. The investigation/study coordinator will be responsible for entering the subject's identification (treatment/randomization number), treatment period, and other pertinent subject information before giving the SMD to the subject. The subject will be instructed to record dates/times and the number of tablets/capsules of study drug doses (Note: RBV is a rescue medication and should be reported as a concomitant medication; it should not be reported on the SMD.) on the SMD for the entire time period. Only the subject should enter information on the SMD. The subject is to return the completed SMD at each scheduled visit. At all visits during the treatment period, site personnel must verify the accuracy of the SMD by comparing entries with amounts of unused study drug. If a discrepancy is noted, investigator/study coordinator must discuss the discrepancy with the subject, and the explanation must be documented. Only the subject shall make any changes to the entries on the SMD. The subject will initial the SMD to confirm that the information is accurate. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary onto the appropriate case report form (CRF).

Interruptions from the protocol specified treatment plan, as outlined in Section 5.2, require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff at the Day 1 visit.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations must be performed by the principal investigator or sub-investigator (physician, physician assistant, or nurse practitioner).

A complete physical examination, performed at the Screening visit, includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic examinations should be performed when clinically indicated. For all other visits, a focused physical examination will be performed when clinically indicated. Any significant changes between the screening visit and other physical examinations performed prior to the initiation of therapy should be noted in the Medical History electronic CRF (eCRF). Any significant changes after receiving study drug at Day 1 must be reported as AEs and entered on the AE eCRF. If a subject is discontinued for any reasons during the treatment period, every attempt should be made to perform a final physical examination.

7.1.2.2 Weight and Height Assessment

The subject's weight and height should be assessed as mentioned in the Trial Flow Chart (Section 6.0). Clinically significant changes from Day 1 in weight should also be captured as AEs in the eCRF.

7.1.2.3 12-Lead ECG

Special care must be taken for proper lead placement. Subjects should be shaved as necessary for proper lead placement. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. However, clinically significant findings from the screening ECG must be captured in the medical history eCRF. For ECGs performed during treatment or during the follow-up period, any clinically significant changes compared with the screening ECG must be captured as AEs.

All subjects will have 12-lead ECGs performed at screening, Day 1, TW2, TW4, TW8, TW12, FW4, and FW12. In addition, the subset of subjects in the Intensive PK/PD group will also have 12-lead ECGs performed at Day 3 and Day 7.

7.1.2.4 Vital Signs

Vital signs will include heart rate, blood pressure, and oral temperature. Subjects should be resting in a semi-recumbent or sitting position for at least 10 minutes prior to having vital sign measurements obtained.

Oral temperatures should be taken, but if oral is not possible, a tympanic, rectal, or axillary temperature may be taken (note: temporal is allowed).

After the screening visit, the site should indicate whether or not the result is clinically significant and if any subsequent changes constitute an AE.

7.1.2.5 Birth Control Confirmation

Care must be taken to avoid pregnancy in female subjects of childbearing potential, and for the female partners of childbearing potential of male subjects, who have their treatment regimen with MK-3682 + RZR extended to 16 weeks' duration and RBV added to the regimen.

Confirmation must be obtained by site personnel that subjects and their partner(s) are using acceptable methods of contraception (see Subject Inclusion Criteria, Section 5.1.2). This assessment must be documented in the subject's study chart at each specified visit (see Trial Flow Chart, Section 6.0).

7.1.2.6 Adverse Events

Refer to Section 7.2 for details on assessing and recording AEs.

7.1.2.7 Noninvasive Methods of Cirrhosis Evaluation

FibroScan®: This method for assessing liver cirrhosis has gained increasing acceptance. In the US, this methodology is Food and Drug Administration (FDA) approved and, in other countries, it is often the preferred method of assessment. FibroScan® results are influenced by a number of confounders including ALT, ascites, and underlying disease. Hepatitis C is one of the best studied and is the disease state with the most reproducible/reliable results. FibroScan® has been evaluated in many liver diseases for the staging of liver fibrosis, and has been demonstrated to be very effective for differentiating cirrhosis (F4) from no cirrhosis (<F4), but it is less capable of differentiating gradations of fibrosis. In a large study by Castera, et al [40], a population of patients with chronic HCV infection, a cutoff of 12.5 kPa was selected for cirrhotics. At this cutoff, the sensitivity and specificity of the test for cirrhosis were 87% and 91%, respectively, and the negative predictive value was 95%. Since this analysis was assessed specifically in subjects with chronic HCV infection, the cutoff value >12.5 kPa used by Castera was selected to include cirrhotics in the current study.

FibroTest® + APRI: Various methodologies have been developed in order to improve the sensitivity and specificity of blood tests used to diagnose cirrhosis in patients with chronic HCV infection. One such algorithm, the sequential algorithm for fibrosis evaluation (SAFE), which uses a combination of FibroTest® and the APRI, is very accurate for diagnosing cirrhosis [41]. For cirrhosis, the SAFE for F4 algorithm provides a diagnostic accuracy of 89.5% with a negative predictive value of 94.6%. Using this algorithm, it is estimated that only 6.2% of the patients would need a liver biopsy to confirm the diagnosis of cirrhosis. The cutoff values for excluding cirrhotics using the 2 tests, without the use of liver biopsy, are ≤1 and ≤0.48 for FibroTest® and APRI when the SAFE for F4 is used. This study uses this method with one variation, which is the more stringent requirement that both the APRI and FibroTest® need to be consistent with no cirrhosis (i.e., APRI is ≤1 AND FibroTest® ≤0.48).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below (see Table 12). The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue

volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 12. Sample collection, storage and shipment instructions will be provided in the operations/laboratory manual.

Table 12 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Bilirubin	HCV GT
Hemoglobin	ALP	Blood	HIV-1 and HIV-2 serology (screening only)
Platelet count	ALT	Glucose	PT/INR
WBC (total and differential)	AST	Ketone	PTT
Erythrocytes (RBC count)	Creatinine	Leukocyte esterase	Choriogonadotropin beta (Urine pregnancy test kits to sites)
	Creatinine clearance (eGFR)	Nitrites	Serum human chorionic gonadotropin (reflex when urine pregnancy test is "positive")
	Creatine kinase	pH	Plasma HCV RNA
	Gamma-glutamyltransferase	Protein	Fibrosure® (Fibrotest) as requested by site for entry criteria (may be performed locally)
	Glucose (serum glucose)	Specific gravity	APRI calculation (screening only)
	Amylase	Bacteria	CD4+ T-cell count (at screening in all subjects, then in HIV/HCV coinfected subjects only at subsequent visits)
	Lipase	Squamous epithelial cells	Plasma HIV-1 RNA (at screening in all subjects, then in HIV/HCV coinfected subjects only at subsequent visits)

Hematology	Chemistry	Urinalysis	Other
	Potassium	RBC	HBsAg (at screening in all subjects, then at certain subsequent visits for subjects who are anti-HBc positive)
	Sodium	WBC	Anti-HBc (screening only)
	Total bilirubin		Anti-HBs (screening only)
	Direct bilirubin		HBV DNA (for subjects who are anti-HBc positive, at screening and at certain subsequent visits)
	Indirect bilirubin		
	Total protein		
	Blood urea nitrogen		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; Anti-HBc = hepatitis B core antibody; Anti-HBs = hepatitis B surface antibody; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GT = genotype; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell count.

Subjects should be fasted for all on-treatment visits to allow for appropriate PK analysis.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of PK will be collaboratively determined by the Departments of Quantitative Pharmacology and Pharmacometrics (QPP) and the appropriate department within Clinical Research. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers. The time points for both PK and viral kinetic sample collection are detailed in Table 13.

7.1.3.2.1 Pharmacokinetics: Blood Collection for Plasma MK-3682 (and Metabolites), and Ruzasvir

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

Sample Collection

Pharmacokinetic samples will be collected from all enrolled subjects according to the PK sampling schemes shown in Table 13.

- Subjects in the Intensive PK/PD Group will be providing additional PK samples on Day 3 (pre-dose) and on Day 7 (post-dose) that are not being collected from the other subjects in the study.

Dosing and Sample Collection Instructions

- As specified previously in Section 5.2.2, Timing of Dose Administration, all doses of MK-3682 and RZR should be taken on an empty stomach after an overnight fast, at least 1 hour before the morning meal, with water but without food.
- On all PK visits where a pre-dose sample will be collected, the visit should occur prior to the subject's regular time for taking their study medication and the subject should withhold their dose until after the visit.
- For pre-dose PK visits after Visit 2 (Day 1), if this visit time is not feasible, the subject should be instructed to take their study medication as per their regular schedule. PK samples should still be collected during the visit.

Note: While every effort should be made to schedule visits with PK draws so that they occur within the window specified in Table 13; when this is not possible, the PK samples should still be collected even if out of window.

- The date and time of each PK sample as well as the date and time of the last dose of MK-3682 and RZR prior to the PK sample will be recorded.

Recording and Entering Meal Information

- Subjects will be provided with a meal diary with instructions for recording meal data that includes what they eat/drink and the time of the meal. Subjects should record ALL meal data from 48 hours BEFORE the PK visit through the day of the PK visit.
- The site will be responsible for entering the appropriate data from the meal diary, as well as the qualitative fat content of the meal, in the eCRF according to the eCRF Entry Guidelines. Meal data should be entered by the site as follows:
    - For visits where only a predose PK sample is collected, enter meal data for up to **5 hours before, and up to 2 hours after** the MK-3682 and RZR dose administered on the day **prior** to the predose PK visit.
    - For visits where a postdose PK sample is also collected, also enter meal data for up to **5 hours before, and up to 2 hours after** the MK-3682 and RZR dose administered at the study site.
    - For subjects who may take multiple meals during the time window, only the meal closest to the last dose prior to the PK samples will be entered.

Table 13 Pharmacokinetic and Pharmacodynamic Sampling Time Points

Visit Number	Study Day/Week	Time Relative to Dose of MK-3682/ RZR [1, 2]	All Subjects	Intensive PK/PD Group Subjects	
			PK Time Points for MK-3682 and RZR	**PK** Time Points for MK-3682 and RZR	**PD (Viral Kinetic)** Time Points
2	Day 1	Predose	X	X	X
2-3	Day 1 – Day 2	2, 4, 8, 12, 24, and 32 hours postdose	n/a	n/a	X
4	Day 3	Predose	n/a	X[3]	X
5	Day 5	n/a	n/a	n/a	X
6	Day 7	Predose	X	X[3]	X
		0.5-, 2-, and 4-hour postdose	n/a	X[3]	n/a
7	Week 2	Predose	X	X	n/a
8	Week 4	Predose	X	X	n/a
		0.5- and 2-hour postdose	X	X	n/a
9	Week 6	Predose	X	X	n/a
10	Week 8	Predose	X	X	n/a
12	Week 12	Predose	X	X	n/a
14	Week 16[4]	Predose	X	X	n/a
21	HCV/HIV Viral Failure Confirmation Visit[5]	n/a	X[5]	X	n/a
22	Early Discontinuation Visit[5]	n/a	X[5]	X	n/a

ECG = electrocardiogram; HCV = hepatitis C virus; HIV = human immunodeficiency virus; n/a = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RZR = ruzasvir.

[1] Time relative to last dose of MK-3682 and RZR must be recorded in the electronic case report form.

[2] After study Visit 2, if there are cases in which a morning visit is not feasible and a subject is seen in the afternoon, the subject should take their study medication in the morning, after an overnight fast, as per their regular schedule (in accordance with Section 5.2.2 Timing of Dose Administration) and PK samples will still be collected during these visits.

[3] ECGs will be collected on ALL subjects on screening, Day 1, TW2, TW4, TW8, TW12, FW4 and FW12; Additional ECGs will be collected on subjects in the Intensive PK/PD Group subjects on Day 3 and Day 7.

[4] Week 16 only applies for those subjects whose treatment duration may be extended. **PK sampling scheme for these subjects remain the same with the addition of TW16 time point.**

[5] PK samples and meal information for PK are to be collected at HCV/HIV viral confirmation or early discontinuation visits that occur only during the study treatment period.

Note: Approximately 4 mL of blood will be collected at each specified time point for plasma PK assessment of MK-3682 (and metabolites).
Approximately 4 mL of blood will be collected at each specified time point for plasma PK assessment of RZR.

Note: The date and time of the PK sample collection for all MK-3682 (and metabolites) and RZR PK samples must be recorded in the electronic case report form.

Note: At the time of PK sample collection, subjects will be asked to provide information regarding the time/date of the last MK-3682 and RZR dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary.)

7.1.3.2.2 Pharmacodynamics: Viral Kinetics

HCV RNA samples also will be collected at the Week 1, 2, 4, 6, 8, 10 and 12 visits for all subjects during treatment (and Week 14 and 16 visits for subjects whose treatment duration may be extended). Additional samples for HCV RNA will be collected on a subset of subjects in the Intensive PK/PD group (see Table 13). The data from this sub-study will be used to validate the existing viral dynamics model for MK-3682 and RZR. A total of approximately 30 subjects, the first 5 subjects for each GT1-6 who consent to participate, will undergo additional PK and PD evaluations and have electrocardiographs (ECGs) performed.

See Section 6.0 Trial Flow Chart and Table 13 for detailed information on sample collection and visits.

7.1.3.3 HCV Evaluation

The following specimens are to be obtained for HCV evaluation as part of efficacy/pharmacogenetic measurements:

- Samples for HCV GT evaluation must be obtained for inclusion in the study. All baseline samples will be genotyped using the FDA-approved Abbot HCV Real Time Genotype II assay that detects HCV GTs 1a, 1b, 2, 3, 4, 5, and 6 through the use of GT-specific fluorescent-labeled oligonucleotide probes in a real-time reverse transcription polymerase chain reaction (RT-PCR) assay. The RT-PCR reaction uses 3 sets of HCV-specific amplification primers targeting the 5'untranslated region (UTR) (for all GTs) and NS5B regions from GT1a and 1b. The assay has accuracy of >96% for GT1, 1a, 1b, 2, 3, and 5; 89% for GT5, and 83% for GT6; with 100% specificity in HCV serologically negative plasma samples.
- Blood must be drawn from each subject to assess HCV RNA plasma levels at various time points as shown in the Trial Flow Chart (Section 6.0). HCV RNA in plasma will be measured using a COBAS™ AmpliPrep/COBAS™ Taqman HCV Test, version 2.0® assay with an LLOQ of 15 IU/mL. Leftover plasma may be used for viral resistance testing if needed. Also, leftover plasma may be used for FBR only if the subject signed for FBR consent.
- Blood must be drawn from each subject to assess viral resistance mutation and processed as instructed by the central laboratory manual. Leftover plasma may be used for FBR only if the subject signed for FBR consent.
- Protein and metabolites may be measured from blood samples to compare biomarkers measured prior to treatment to biomarkers measured at several time points during treatment that correlate with subject response to treatment (e.g., sustained viral response).
- Samples collected for genetic analysis are obtained at Day 1. Any leftover DNA may be used for FBR only if the subject signs for FBR consent.

NOTE: Samples may also be used for future assay development and validation if the subject signed for FBR consent.

7.1.3.4 HIV Evaluation

The following specimens are to be obtained for HIV evaluation:

- Blood must be drawn from each subject to assess HIV RNA plasma levels at screening as shown in the Trial Flow Chart (Section 6.0). HIV RNA in plasma will be measured using a COBAS™ AmpliPrep/COBAS™ TaqMan HIV-1 Test, version 2.0® assay with a LLOQ of 20 IU/mL.
- Blood must be drawn from each subject with HIV co-infection to assess immunologic status. CD4+ T-cell counts will be obtained at screening as shown in the Trial Flow Chart (Section 6.0).
- In the event of HIV virologic breakthrough, a sample for HIV viral resistance is to be collected at the viral failure confirmation visit.

The following nomenclature will be used when describing HIV RNA levels:

- HIV-1 RNA <LLOQ, TND
- HIV-1 RNA <LLOQ, Target Detected
- HIV-1 RNA IU/mL

7.1.3.5 HBV Evaluation

- Blood must be drawn from each subject to assess HBsAg, anti-HBc, and anti-HBs at screening.
- For subjects who are anti-HBc positive, HBV DNA will be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial. The results of these assessments will be used to determine HBV reactivation, which will be reported as an Event of Clinical Interest as specified in Section 7.2.3.2.
- Subjects who develop HBV reactivation will be managed by site investigators according to current treatment guidelines and/or local standard of care.
- Subjects who develop HBV reactivation may continue in the trial at the discretion of the site investigators.

7.1.3.6 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the laboratory manual.

7.1.3.7 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main study plasma from HCV RNA stored for future research
- Leftover main study plasma from viral resistance and biomarkers stored for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

The subjects who are participating in the Intensive PK/PD group will report to the clinical research unit (CRU) on the morning of Day 1 prior to trial drug administration and will remain either in the unit or in a local facility until completion of the 32-hour blood draw after the first dose of study medication. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or

reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

none

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Within 45 days prior to allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Verification should be obtained to confirm the subject's cirrhosis status and the subject's fibrosis score must be captured to support secondary data analysis. The investigator will discuss with each potential subject the nature of the study, its requirements, and its restrictions. Screening procedures may be repeated after consultation with the Sponsor.

Subjects will be instructed that they are required to use an acceptable method of birth control (see Subject Inclusion Criteria Section 5.1.2) from at least 2 weeks prior to Day 1, throughout treatment, and for 14 days after the last dose of study medication, or if a subject's treatment duration is extended with MK-3682 + RZR + RBV, for 6 months after the last dose of study medication, or longer if dictated by local regulations.

Subjects will be instructed about the restrictions for concomitant medications, as noted in Section 5.5.

All screening procedures listed for Visit 1 in the Trial Flow Chart must be completed and subject eligibility confirmed by the investigator prior to the subject's allocation and drug administration.

All subjects will be given a Subject Identification Card (Section 7.1.1.3), at the time of screening, identifying them as participants in a research study. The Subject Identification Card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

7.1.5.2 Rescreening

Subjects who have previously completed the screening visit (Visit 1) and were deemed eligible for randomization/allocation into this study, but failed to be randomized or allocated within the 45-day window, may be rescreened to re-evaluate study eligibility. To reconfirm the subject's eligibility, all pre-study evaluations should be repeated, after approval from the Sponsor, except for the following:

- HCV GT determination
- Hepatitis B virus screening

- HIV-1 serology
- Liver biopsy/Fibroscan/ FibroSure® (Fibrotest®)
- Liver imaging
- 12-lead ECG

If any of the laboratory, ECG, or Fibroscan exclusion criteria are met, the site may have the abnormal value retested one time.

7.1.5.3 Treatment Period

Treatment Day 1 (Visit 2)

Subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2).

Pre- and Post-Treatment Procedures

Day 1 procedures listed on the Trial Flow Chart should be performed prior to dosing unless specified otherwise. For female subjects of reproductive potential, a urine pregnancy test will be performed at the site prior to study drug initiation. If the urine pregnancy test result is negative, the subject will be eligible for allocation and the remainder of the pretreatment (Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, a serum pregnancy test will be performed. If the result of the serum pregnancy test is positive, the subject must not be randomized or allocated to treatment in the study.

Blood and urine will be collected for assay of safety evaluations, including plasma HCV RNA, plasma HIV RNA (only for HIV co-infected subjects), and PK measurements. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) set forth in the manual(s).

Additional samples will be collected for genetic evaluation of host parameters related to the response of HCV subjects to MK-3682 and RZR.

7.1.5.4 Drug Administration

Following completion of the Day 1 procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the interactive voice response system/interactive web response system (IVRS/IWRS) for assignment of the drug regimen to be administered and duration of treatment. Sites should not call IVRS for drug administration until the subject has met all criteria for the study and are ready to receive the first dose of study medication on Day 1.

The first dose of prescribed study medications should be administered at the Day 1 visit. Study medications should be taken on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Study medications should be taken with water but without food. In addition, subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2) and for all other visits at which a pre-dose PK sample is to be collected. All other dosing after the Day 1 visit will be performed by the subject (i.e., unsupervised at his/her home) and recorded on the subject's SMD provided during the visit.

Subjects should complete study therapy as defined by their assigned treatment regimen and per Section 5.2.

Additional instructions related to drug administration on PK visit days are provided in Section 7.1.3.2.1.

7.1.5.5 Follow-up Visits

At the completion of study therapy, subjects will return to the study site for follow-up visits at 4, 8, 12, and 24 weeks after the last dose of study drug. Follow-up visits at 16 and 20 weeks after the last dose of study drug will be virtual visits, meaning site personnel will have telephone contact with the subject to make sure that he/she is doing well and to give a reminder for the Follow-up Week 24 visit.

7.1.5.6 Discontinued Subjects Continuing to be Monitored in the Trial

Discontinuation During Treatment Period

Subjects who discontinue therapy in the trial prior to the last scheduled treatment visit should have an Early Discontinuation visit and then continue into follow-up visits.

At a minimum, the following information should be collected:

- The reason the subject discontinued
- The date of the last dose of study medications from the trial
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate
- (Serious) Adverse events (per reporting requirements outlined in Section 7.2)

Final assessments:

- Every effort should be made to ensure that all procedures and evaluations scheduled for the Early Discontinuation Visit are performed.
- Retrieve all study medications from the subject.

Discontinuation for Virologic Failure

Subjects who discontinue because they have met criteria for virologic failure (Section 4.2.5.1.1.2) while on study therapy should complete an Early Discontinuation Visit as outlined in the Trial Flow Chart (Section 6.0) and return to the study site for follow-up visits at 4, 8, 12, and 24 weeks following confirmation of virologic failure.

Subjects who meet the virologic failure criterion for relapse (HCV RNA ≥LLOQ following the end of all study therapy, after becoming undetectable [TND] at the end of treatment) will return to the study site for the remainder of their follow-up visits (e.g., 4, 8, 12, and 24 weeks) as outlined in the Trial Flow Chart (Section 6.0).

Discontinuation During Follow-Up Period

Subjects who discontinue during the follow-up period (e.g., follow-up visits at 4, 8, 12, and 24 weeks after end of treatment) for reasons other than virologic failure should complete an Early Discontinuation Visit as outlined in the Trial Flow Chart.

At a minimum, the following information should be collected:

- The reason the subject discontinued
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate
- SAEs (per reporting requirements outlined in Section 7.2)

7.1.5.7 Evaluation of Laboratory Safety Signals

Laboratory safety measurements will be evaluated throughout the study to assess potential safety signals as outlined in the Trial Flow Chart (Section 6.0).

If a subject has 1 or more of the laboratory ECI criteria (Section 7.2.3.2) at the last dosing visit, then the subject should return to the site weekly for additional monitoring until the values normalize.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a

procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose in excess of the prescribed dose of MK-3682 or RZR. For RBV, overdose is a dose that exceeds 1600 mg/day.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product or that occur through 6 months (or longer if dictated by local regulations) for subjects receiving a ribavirin-containing regimen must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 14 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. first instance of ALT or AST >500 IU/L from the initiation of study therapy through 14 days following treatment.*
3. first instance of ALT or AST >3x nadir AND >3X ULN from the initiation of study therapy through 14 days following treatment.*

*Note: The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require and additional evaluation for an underlying etiology. The trial site guidance for assessment and the follow up of these criteria can be found in the Investigator Trial File Binders (or equivalent)

4. first instance of eGFR <50 mL/min/1.73 m^2 from the initiation of study therapy through 14 days following treatment. Creatinine clearance will be evaluated as an estimated GFR (eGFR), based on the modification of diet in renal disease (MDRD) equation:

   eGFR (mL/min/1.73 m^2) = 175 × (Scr, std)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if black)

   Scr, std: serum creatinine measured with a standardized assay
5. first instance of serum creatinine Grade 2 or higher (>1.3 × ULN) and elevated from baseline from the initiation of study therapy through 14 days following treatment.
6. HBV reactivation defined as either:
   a. sero-reversion from HBsAg negative to HBsAg positive, OR

b. detectable HBV DNA in subjects who were previously undetectable or ≥1 log increase in HBV DNA from baseline.

Note: As detailed in Section 7.1.3.5, subjects who develop HBV reactivation will be managed by site investigators according to current treatment guidelines and/or local standard of care. Subjects who develop HBV reactivation may continue in the trial at the discretion of the site investigators.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 14. The investigator's assessment of causality is required for each adverse event. Refer to Table 14 for instructions in evaluating adverse events.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 14 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12.

Study Design Overview	This is a Phase 2, nonrandomized, multi-site, open-label trial to study the efficacy and safety of the combination regimen of MK-3682 + RZR in subjects with chronic HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection. All subjects will receive MK-3682 450 mg + RZR 180 mg for 12 weeks. Subjects can be treatment-naïve or treatment-experienced with a prior IFN-based therapy, cirrhotic or non-cirrhotic, and mono-infected with HCV or co-infected with HIV. Approximately 250 subjects will be assigned to receive treatment, with target allocation based on GT (GT1, GT2, GT3, GT4, GT5, or GT6). All subjects will be followed for 24 weeks after the end of study therapy.
Treatment Assignment	All subjects will receive MK-3682 + RZR for 12 weeks.
Analysis Populations	Efficacy: Full Analysis Set (FAS), Per Protocol (PP), and modified Full Analysis Set (mFAS). Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Proportion of subjects achieving SVR_{12}
Key Secondary Endpoints	Proportion of subjects achieving $SVR_{24;}$ Proportion of subjects experiencing virologic failure at FW12 among all subjects who do not discontinue study for non–treatment-related reasons.
Statistical Methods for Key Efficacy Analyses	For the primary efficacy analysis based on the FAS population, the proportions of subjects achieving SVR_{12} will be estimated in each GT, and 95% confidence intervals (CIs) for these rates will be calculated using the Clopper-Pearson method [42]. The missing data approach of Missing=Failure (M=F) will be utilized for the primary analysis. The same Clopper-Pearson method will be used to analyze all binary endpoints based on the mFAS population and for the PP population for each GT, and Treatment-Related Discontinuation=Failure (TRD=F) will be used as the missing data approach for both analysis populations.

Statistical Methods for Key Safety Analyses	The ASaT population will be used for safety analyses. The proportion of subjects with AEs of elevated laboratory values that are reported as ECIs (as described in Section 7.2.3.2) during the study therapy period will be provided along with the corresponding 95% CIs. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, an SAE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized in the same manner.
Interim Analyses	An assessment of safety for the first 50 subjects will be made. (See Section 5.11.1 for the criteria for assessing safety in the first 50 subjects.) In addition, an assessment for efficacy will be made for the first 10 per-protocol subjects enrolled in each GT, and on an ongoing basis to determine whether there is a need to modify the treatment regimen. (See Section 5.11.4 for the criteria for assessing efficacy and the initiation of treatment modifications). Finally, throughout the course of this open-label study, efficacy and safety will be monitored for trends and programmatic decisions.
Multiplicity	No multiplicity adjustment is planned for the study.
Sample Size and Power	Approximately 250 subjects will be allocated to treatment, with 35 GT1a-, 15 GT1b-, 50 GT2-, 50 GT3-, 50 GT4-, 25 GT5- and 25 GT6-infected subjects. If the SVR_{12} rate is approximately 97.1% for GT1a (34 successes out of 35), the exact 95% CI is (85.1, 99.9). If the SVR_{12} rate is approximately 93.3% for GT1b (14 successes out of 15), the exact 95% CI is (68.1, 99.8). For GT2, GT3, and GT4 where 50 subjects are targeted for treatment allocation, if the SVR_{12} rate is 98% (49 successes out of 50), the exact 95% CI is (89.4, 99.9). If the SVR_{12} rate is 94% (47 successes out of 50), the exact 95% CI is (83.5, 98.7). For GT5 and GT6 where 25 subjects are targeted for treatment allocation, if the SVR_{12} rate is 96% (24 successes out of 25), the exact 95% CI is (79.6, 99.9). If the SVR_{12} rate is 92% (23 successes out of 25), the exact 95% CI is (74.0, 99.0). Detailed information for varying SVR rates is in Section 8.9.1.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This trial is being conducted as an open-label study, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed in Section 8.4.1.

8.4.1 Efficacy/Pharmacokinetics Endpoints

8.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.5.1.

The primary efficacy endpoint is the proportion of subjects achieving SVR_{12}.

The secondary efficacy endpoints are the following:

1. The proportion of subjects achieving SVR_{24};
2. The proportion of subjects experiencing virologic failure (either on-treatment failure or relapse post-treatment) through FW12 among all subjects who do not discontinue study for non–treatment-related reasons.

8.4.1.2 Pharmacokinetics Endpoints

Additional details are in Section 4.2.5.3.

The primary PK endpoint for MK-3682 (and metabolites) and RZR is C_{trough}.

8.4.1.3 Exploratory Endpoints

1. The emergence of RAVs to MK-3682 or RZR when administered as part of a combination regimen.
2. The proportion of subjects with HCV RNA <LLOQ (either target detected but unquantifiable [TD(u)] or TND) at TW4, TW8, end of treatment, FW4, and FW8.
3. The collection of the viral kinetics in a subset of subjects will be used to explore the impact of early viral load decline on sustained viral response in each treatment arm.
4. The relationship between genetic variation, including but not limited to variation in IL28B, and response to the treatment administered and mechanisms of disease. Variation across the human genome will be analyzed for association with clinical data collected in this study.
5. The proportion of HIV co-infected subjects who develop HIV-1 virologic failure during protocol therapy.
6. Change from baseline in CD4+ T-cell counts in the HIV co-infected population.
7. The proportion of anti-HBc positive subjects at screening who develop HBV reactivation (see Section 7.2.3.2).

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.5.2 and ECIs are defined in Section 7.2.3.2.

8.5 Analysis Populations

If the need arises to extend the treatment duration to 16 weeks and add RBV to the treatment regimen, data displays for both efficacy and safety will be adjusted to reflect the actual treatment received.

8.5.1 Efficacy Analysis Populations

Full Analysis Set (FAS)

The FAS population will serve as the primary population of efficacy data in this study. The FAS population consists of all subjects who are assigned to treatment and receive at least 1 dose of study treatment in this study.

Per Protocol (PP)

The PP population will serve as a supportive analysis population. The PP population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints. Non-virologic failures that are due to administrative (non-treatment-related) reasons will be excluded. Potential violations that may result in the exclusion of a subject from the PP population also include the following:

- The subject did not meet specific inclusion/exclusion criteria (for example, the subject is infected with a mixed GT infection or non-typeable GT).
- The subject received concomitant medications that are prohibited due to their potential to result in a clinically significant lowering of the MK-3682 or RZR concentrations (see Section 5.5 for specific details of prohibited medications). Further, any co-administered medication currently unidentified, but for which subsequent clinical drug-drug interaction data indicate that co-administration with MKs leads to a clinically significant lowering of MK concentrations, may also exclude a subject from the per-protocol population..
- Other violations may be identified during the course of data collection and they will be listed specifically in the CSR.

A subject with important deviations from the protocol at treatment allocation (Day 1) will be excluded from the PP population. For subjects with important deviations from the protocol as described above during the course of treatment, data obtained subsequent to the violation will be excluded from analysis.

Modified Full Analysis Set (mFAS)

The mFAS population will be used for supportive analysis of the efficacy endpoints of SVR_{12} and SVR_{24} and as primary analysis for the endpoint of the proportion of subjects experiencing virologic failure at FW12 as a primary analysis. The mFAS population is a subset of the FAS population, with subjects excluded for study discontinuation for reasons unrelated to the treatment regimen. Examples include loss to follow-up, discontinuation from the study due to non-drug related AEs, informed consent withdrawal, and other non-virologic failures.

The final determination on the exclusion of subjects from various analysis populations will be made prior to the final database lock and will be documented in a separate memo. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Population

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. In this study with a single treatment regimen, the ASaT population is the same as the FAS population. For reporting consistency, the terms FAS for efficacy and ASaT for safety will be maintained.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

There will be no statistical testing conducted to address the objectives of this study. A summary of the analysis strategy for efficacy variables is shown in Table 15. The analysis strategy for safety is described in Section 8.6.2.

8.6.1 Statistical Methods for Efficacy Analyses

Missing Values

A missing data point for a given study visit may be due to any one of the following reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a subject discontinued from the study before reaching the visit. Subjects who prematurely discontinued the assigned treatment are encouraged to remain in the study for follow-up, if possible.

The HCV RNA outcome is categorized as TND, TD (u), and TD (q). There are 3 types of missing data handled by different approaches.

1. Intermittent missing: If a missing data point is immediately preceded and followed by non-missing HCV RNA outcomes, the missing value would be imputed to the worst outcome of the two. For example, if a missing data point is preceded by TD(q) and followed by TD(u) or TND, then the missing value would be imputed as TD(q); if a missing data point is preceded by TD(u) and followed by TND, then the missing value would be imputed as TD(u); when a missing value is flanked by two TND, then the missing value would be imputed as TND.
2. Non-intermittent missing related to the study drug: For missing values due to premature study discontinuations due to treatment-related reasons either for safety or efficacy, the missing values will be considered as treatment failures.
3. Non-intermittent missing for reasons unrelated to the study drug: For missing data due to premature study discontinuations with reasons unrelated to treatment such as loss to follow-up, protocol deviation, withdrawal of consent, administrative reasons, etc., the missingness mechanism is unlikely to be related to subjects' response to the HCV treatment, and therefore the missing at random assumption is reasonable.

The following 2 approaches will be used to handle non-intermittent missing data due to premature discontinuations, depending on the analytical strategy, as described in the section below and in Table 15.

1. Treatment-Related Discontinuation=Failure (TRD=F) approach: Subjects with treatment-related missing data (type #2 above) will be considered as failure; whereas the subjects who have the non-treatment-related missing value (type #3 above) and who do not have virologic failure during the observed study period will be excluded from the analysis for the time points following their study withdrawal. Note that subjects with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are classified as failures.
2. Missing=Failure (M=F) approach: Subjects with any non-intermittent missing data (i.e., type #2 and #3 above) will be imputed as failures, regardless of the reason for study discontinuation.

In addition, a missing baseline/Day 1 HCV RNA result will be replaced with a screening result, if available.

Proportions of Subjects With Virologic Responses and Virologic Failures

For the primary efficacy analysis, the proportions of subjects achieving SVR_{12} for each GT will be provided and 95% CIs for these rates will be calculated using the Clopper-Pearson method [42]. The same method will be used to analyze all binary endpoints including SVR_4, SVR_8, SVR_{24}, and virologic response rates at TW4, TW8, and end of treatment.

For the primary analyses using the FAS population, the M=F missing data approach will be utilized. In these analyses, only subjects with HCV RNA levels <LLOQ for any type of HCV infection at a given time point will be considered to have achieved the endpoint.

For all analyses conducted using the PP and mFAS populations, the missing data approach of TRD=F will be utilized. In addition, for all analyses based on these 2 populations, a subject will be considered to have achieved a response for a particular endpoint if the HCV RNA levels for the infection he/she had at baseline are <LLOQ. For example, if a subject has HCV RNA levels ≥LLOQ at a particular time point, but those RNA levels correspond to an infection that is of a different GT and/or subtype compared to the infection detected at baseline and the baseline infection has been cleared, then the subject is considered to have achieved response for the given endpoint.

To estimate the secondary efficacy endpoint of proportion of subjects experiencing virologic failure at FW12 for each GT, 95% CIs for these rates will be calculated in the mFAS analysis population using the Clopper-Pearson method [42]. The missing data approach of TRD=F described previously will be utilized for this analysis.

Table 15 includes a summary of the key efficacy analyses, and Table 16 includes a summary of the analysis populations and various criteria to assess the primary endpoint (SVR_{12}) and secondary endpoints (SVR_{24} and proportion of subjects experiencing virologic failure at FW12).

Table 15 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Proportion of subjects achieving SVR_{12} by genotype	P	95% CI (Clopper-Pearson)	FAS	M=F
Proportion of subjects achieving SVR_{12} by genotype	S	95% CI (Clopper-Pearson)	mFAS	TRD=F
Proportion of subjects achieving SVR_{12} by genotype	S	95% CI (Clopper-Pearson)	PP	TRD=F
Secondary				
Proportion of subjects achieving SVR_{24} by genotype	P	95% CI (Clopper-Pearson)	FAS	M=F
Proportion of subjects achieving SVR_{24} by genotype	S	95% CI (Clopper-Pearson)	mFAS	TRD=F
Proportion of subjects achieving SVR_{24} by genotype	S	95% CI (Clopper-Pearson)	PP	TRD=F
Proportion of subjects experiencing virologic failure at FW12 by genotype	P	95% CI (Clopper-Pearson)	mFAS	TRD=F

CI = confidence interval; FAS = Full Analysis Set; M=F = Missing=Failure; mFAS = modified Full Analysis Set; P = primary approach; PP = Per Protocol; S = secondary approach; TRD=F = Treatment-Related Discontinuation=Failure.

Table 16 Analysis Populations, Criteria for Response, Non-Response, and Exclusion from Analysis Populations

Analysis Population	Criteria for Response	Criteria for Non-Response	Criteria for exclusion from analysis population
FAS (Primary for SVR_{12} and SVR_{24})	HCV RNA < LLOQ	HCV RNA ≥ LLOQ	Subject did not receive at least 1 dose of study medication
PP (Supportive for SVR_{12} and SVR_{24})	HCV RNA < LLOQ for baseline infection[1] HCV RNA ≥ LLOQ demonstrated to be due to reinfection (detectable HCV RNA for a viral strain other than that detected at baseline after clearance of baseline infection[1])	HCV RNA ≥ LLOQ for baseline infection[1]	Subject has important deviations from the protocol including discontinuation from the study for non-treatment related reasons and other violations such as violation of inclusion/exclusion criteria and use of prohibited concomitant medications (see Section 8.5.1)
mFAS (Supportive for SVR_{12}, SVR_{24}; Primary for the proportion of subjects experiencing virologic failure at FW12)	HCV RNA < LLOQ for baseline infection[1] HCV RNA ≥ LLOQ demonstrated to be due to reinfection (detectable HCV RNA for a viral strain other than that detected at baseline after clearance of baseline infection[1])	HCV RNA ≥ LLOQ for baseline infection[1]	Subject discontinued from the study for non-treatment related reasons.

FAS = Full Analysis Set; FW12 = Follow-up Week 12; GT = genotype; LLOQ = lower limit of quantification; mFAS = modified Full Analysis Set; PP = Per Protocol; RNA = ribonucleic acid; SVR_{12} = sustained virologic response after 12 weeks of treatment; SVR_{24} = sustained virologic response after 24 weeks of treatment.
[1] Baseline infection: GT(s) and subtype(s) present at baseline based on sequencing and genotyping assay

Subject Virologic Failure: Non-response, Rebound, Virologic Breakthrough, Relapse and Reinfection

Summary statistics will be provided to describe the rates of occurrence of subject non-response, rebound, virologic breakthrough, and relapse. Definitions for subject non-response, rebound, virologic breakthrough, and relapse are in Section 4.2.5.1.1.2. Reinfection will be defined as having detectable virus of a different GT than that detected at baseline as determined by sequencing. Those with reinfection will be considered treatment success in the mFAS and PP analyses as long as HCV RNA < LLOQ is achieved for the baseline infection.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory parameters. The 95% CIs for the safety parameters will be estimated

using the Clopper-Pearson method [42], which is a conservative exact method of providing CIs in this estimation study.

The analysis of safety parameters will follow a tiered approach (Table 17). The tiers differ with respect to the analyses that will be performed.

The first tier includes (1) AEs of elevated laboratory values that are reported as ECIs described in Section 7.2.3.2; (2) at least 1 AE; (3) a drug-related AE; (4) an SAE; (5) a serious and drug-related AE, and (6) an AE leading to discontinuation. Point estimates and 95% CIs will be provided.

The second tier includes specific AEs by SOC, vital signs, 12-lead ECGs, and standard laboratory safety tests at time points specified in the Trial Flow Chart (Section 6.0). Point estimates will be provided.

Missing safety laboratory, vital signs, or ECG values will be handled using the Data-As-Observed approach, that is, any missing value will be excluded from the analysis. The only exception is when a Baseline/Day 1 result is missing, this will be replaced with the latest pre-treatment result, if available.

Missing safety laboratory, vital signs, or ECG values will be handled using the Data-As-Observed approach, that is, any missing value will be excluded from the analysis. The only exception is when a Baseline/Day 1 result is missing, this will be replaced with the latest pre-treatment result, if available.

The primary safety analysis will summarize the safety data for subjects during the treatment period plus 14 days of follow-up.

Table 17 Analysis Strategy for Safety Parameters

Safety Endpoint[1]	95% CI	Descriptive Statistics
AEs of elevated laboratory values that are reported as ECIs	X	X
Any AE	X	X
Any SAE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Specific AEs, SOCs or PDLCs		X
Change from Baseline Results (laboratory, vital signs, ECG)		X

AE = adverse event; ECG = electrocardiogram; ECI = event of clinical importance; n/a = not applicable; PDLC = pre-defined limit of change; SOC = system organ class; X = results will be provided.
[1] Adverse Experience references refer to both Clinical and Laboratory AEs.

8.6.3 Summaries of Baseline Characteristics, Demographics, and other Analyses

Summaries of demographic and baseline characteristics, PK analyses, and analyses for the exploratory endpoints will be described in detail in the supplementary statistical analysis plan (sSAP).

8.7 Interim Analyses

An assessment of safety for the first 50 subjects will be made when the last of these subjects reaches TW4. The criteria for assessing safety in this cohort of 50 subjects can be found in

Section 5.11.1. Specifically, if >3 out of the first 50 subjects receiving MK-3682 + RZR experience any of the listed criteria, study therapy will be discontinued in all subjects and no additional subjects will be allocated to treatment.

In addition to the safety assessment for the first 50 subjects, criteria for early stopping at any point in the trial is given in Section 5.11.2 and for pausing treatment allocation is given in Section 5.11.3.

An assessment of efficacy will be made when the first 10 per-protocol subjects within each GT (GT1-6) have reached FW4. If ≥3 out of the first 10 subjects in the PP population for each GT (GT1-6) receiving 12 weeks of therapy experience virologic failure (non-response, rebound, breakthrough, or relapse) by FW4, no additional subjects for that particular GT will be allocated to treatment in the trial. Additionally, if the majority of failures are due to relapses (i.e., >50%), the treatment regimen with MK-3682 + RZR for subjects with a particular GT will be extended to 16 weeks' duration and RBV will be added for subjects with this GT who remain on treatment.

In addition, efficacy will continue to be monitored throughout the trial and if >5 of subjects in the PP population for GT1-4, and >3 subjects in the PP population for GT5-6, experience virologic failure at any point in the trial, no additional subjects for that particular GT will be allocated to treatment. Additionally, if the majority of failures are due to relapses (i.e., >50%), the treatment regimen with MK-3682 + RZR for subjects with a particular GT will be extended to 16 weeks' duration and RBV will be added for subjects with this GT who remain on treatment.

Finally, throughout the course of this open-label study, efficacy and safety will be monitored for trends and programmatic decisions.

8.8 Multiplicity

No multiplicity adjustment is planned for the study.

8.9 Sample Size and Power Calculations

8.9.1 Efficacy Analysis

Approximately 250 subjects will be allocated to treatment with a target allocation of 35 GT1a-, 15 GT1b-, 50 GT2-, 50 GT3-, 50 GT4-, 25 GT5-, and 25 GT6-infected subjects. These sample sizes were chosen to provide sufficient confidence of the estimated treatment response rate for the most prevalent GTs (Section 4.2.3)

Table 18 below shows the 2-sided 95% CIs for SVR_{12} under varying assumptions of the number of successes in the FAS population for each GT. Note that these intervals are not symmetric around the point estimate.

Table 18 Two-Sided 95% Confidence Intervals for SVR12 (FAS Population)

Number of subjects in FAS population	Observed Number of Successes (%)	Two-Sided 95% Confidence Interval[1]
15	15 (100.0%)	(78.2, 100.0)
	14 (93.3%)	(68.1, 99.8)
	13 (86.7%)	(59.5, 98.3)
	12 (80.0%)	(51.9, 95.7)
25	25 (100.0%)	(86.3, 100.0)
	24 (96.0%)	(79.6, 99.9)
	23 (92.0%)	(74.0, 99.0)
	22 (88.0%)	(68.8, 97.5)
35	35 (100.0%)	(90.0, 100.0)
	34 (97.1%)	(85.1, 99.9)
	33 (94.3%)	(80.8, 99.3)
	32 (91.4%)	(76.9, 98.2)
50	50 (100.0%)	(92.9, 100.0)
	49 (98.0%)	(89.4, 99.9)
	48 (96.0%)	(86.3, 99.5)
	47 (94.0%)	(83.5, 98.7)

FAS = Full Analysis Set.
[1] Based on the Clopper-Pearson method

8.9.2 Safety Analysis

The primary safety objective of this study will be addressed by a review of the accumulated safety data. Certain safety endpoints of special interest have been identified in Section 8.4.2.

The ASaT population will include approximately 250 subjects. The upper bound of the 95% CI for the underlying percentage of subjects with a specific AE given various hypothetical observed number of subjects with that specific AE within the study are provided in Table 19. These calculations are based on the exact binomial method proposed by Clopper and Pearson [42].

Table 19 Estimate of Incidence of a Specific AE and 95% Upper Confidence Bound Based on a Hypothetical Number of Subjects with that Specific AE

n	Hypothetical Number of Subjects with AE	Estimate of Incidence	95% Upper Confidence Bound[1]
250	0	0.0%	1.5%
	1	0.4%	2.2%
	5	2.0%	4.6%
	10	4.0%	7.2%
	20	8.0%	12.1%
	30	12.0%	16.7%
	40	16.0%	21.1%
	50	20.0%	25.5%

AE = adverse event.
[1] Based on the 2-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934)

8.10 Subgroup Analyses and Effects of Baseline Factors

The subgroup analyses detailed below will be performed within each GT.

To assess the consistency of the response across various subgroups, the SVR_{12} and SVR_{24} rates and associated 95% CIs will be estimated within each category of the following baseline factors as classification variables:

- Presence or absence of baseline RAVs to any of the 2 classes of drugs
- Gender (female, male)
- Age (≥65, <65)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- IL28B GT (CC versus non-CC GT)
- HCV RNA at baseline, ≤800,000 IU/mL versus >800,000 IU/mL; ≤2 million IU/mL versus >2 million IU/mL; ≤10 million IU/mL versus > 10 million IU/mL
- Stage of fibrosis (non-cirrhotic [F0-F3], cirrhotic [F4])
- HIV co-infection status (HCV/HIV co-infected, HCV mono-infected)
- Treatment-experienced and treatment-naïve
- For GT1 subjects: (GT1a vs. GT1b)
- Geographical Region (US, Canada, European Union, Latin America, Asia Pacific, Middle East – note that regions may be collapsed depending on actual enrollment in the trial)

8.11 Compliance (Medical Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each subject, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

A day within the study will be considered an "On-Therapy" day if the subject takes the assigned treatment MK-3682 (450 mg) + RZR (180 mg) as noted in Section 5.2.

For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from allocation to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from allocation to the date of the last dose of study medication.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance for the FAS population.

8.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, and range) for the "Number of Days on Therapy" by dose for each study drug.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 20

Table 20 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3682 150 mg	Tablet	Provided Centrally
RZR 60 mg	Capsule	Provided Centrally
Ribavirin	–	Locally Sourced

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open-label bottles (2 bottles of MK-3682 and 2 bottles of RZR) every 4 weeks during the treatment duration. Each bottle will contain a 2-week supply of study medication. No kitting is required.

If the duration of treatment with MK-3682 + RZR is extended to 16 weeks, sites should dispense RBV (locally sourced).

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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[2] Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. PLoS One. 2014 Jul 28;9(7):e103345.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.7 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

	Screening	Day 1	Day 1-2	Day 3	Day 5	Day 7	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14[1]	Weekj 16[1]	FW 4	FW 8	FW 12	FW 24	**Total Volume**	**Total Volume (if treatment duration extended)**
Test	Approximate Blood Volume (mL)																			
Coagulation (PT, INR)	4.5	4.5				4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	58.5	67.5
HBV Evaluations (HBsAg, Anti-HBc, Anti-HBs, HBV DNA)[3]	10	10						10		10		10		10	10		10	10	80	90
HIV-1/HIV-2 Serology	6																		6	6
Chemistry	10	10				10	10	10	10	10	10	10	10	10	10	10	10	10	130	150
Hematology	3	3				3	3	3	3	3	3	3	3	3	3	3	3	3	39	45
HCV GT Determination	4																		4	4
HCV Viral Resistance and biomarkers		6													6	6	6	6	30	30
MK-3682 PK		4		4[2]		4/16[2]	4	12	4	4		4		4					36/52[2]	40/56[2]
RZR PK		4		4[2]		4/16[2]	4	12	4	4		4		4					36/52[2]	40/56[2]
HCV RNA	6	6	24[2]	6[2]	6[2]	6	6	6	6	6	6	6	6	6	6	6	6	6	78/114[2]	90/126[2]
HIV RNA	6	6				6	6	6	6	6	6	6	6	6	6	6	6	6	78	90
CD4+ T-cell count	6	6				6	6	6	6	6	6	6	6	6	6	6	6	6	78	90
Blood for Genetic Analysis		8.5																	8.5	8.5
Expected Total (mL) Main Study Population	55.5	68	24[2]	14[2]	6[2]	43.5/ 67.5[2]	43.5	69.5	43.5	53.5	35.5	53.5	35.5	53.5	51.5	41.5	51.5	51.5	662/ 730[2]	751/ 819[2]

Anti-HBc=hepatitis B core antibody; anti HBs=hepatitis B surface antibody; GT = genotype; HBsAg=hepatitis B surface antigen; HBV DNA=hepatitis B virus deoxyribonucleic acid; HCV=hepatitis C virus; HIV=Human immunodeficiency virus; INR=international normalized ratio; PK=pharmacokinetic; PT=prothrombin time; RZR = ruzasvir .

[1] **TW14 and TW16 will only occur for those subjects whose treatment duration may be extended.**

[2] Total blood taken from Intensive Evaluation Group.

[3] HBsAg, anti-HBc, and anti-HBs will be assessed at screening in all subjects. For all anti-HBc positive subjects, HBV DNA will also be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial.

12.4 List of Abbreviations and Definition of Terms

Term	Definition
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	American Medical Association
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
APRI	Aspartate aminotransferase to platelet ratio index
ART	Antiretroviral therapy
ASaT	All subjects as treated
AST	Aspartate aminotransferase
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CRU	Clinical research unit
CSR	Clinical study report
CYP	Cytochrome P450
DAA	Direct-acting antiviral therapy
DAO	Data-as-observed
DCV	Daclatasvir
DNA	Deoxyribonucleic acid
EBR	Elbasvir
ECG	Electrocardiogram
ECI	Event of clinical interest
E/CIA	Enzyme or chemiluminescence immunoassay
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERC	Ethics committee
EU	European Union
FAS	Full analysis set
FBR	Future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FU	Follow-up
FW	Follow-up Week
GCP	Good Clinical Practice
GT	Genotype
GZR	Grazoprevir
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

Term	Definition
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IVRS/ IWRS	Interactive voice response system/interactive web response system
LDV	Ledipasvir
LLOQ	Lower limit of quantification
MDRD	Modification of diet in renal disease
mFAS	Modified full analysis set
NGS	Next-generation sequencing
NI	Nucleotide inhibitor
NOAEL	No observed adverse effect level
NS	Nonstructural protein
OMB	Ombitasvir
PD	Pharmacodynamics
PN	Protocol Number
PK	Pharmacokinetics
PP	Per-protocol
PR	Pegylated interferon/ribavirin
QPP	Quantitative pharmacology and pharmacometrics
RAV	Resistance-associated variant
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Real-time polymerase chain reaction
RZR	Ruzasvir
SAE	Serious adverse event
(S)AE	All adverse events, including serious adverse events
SAFE	Sequential algorithm for fibrosis evaluation
SAP	Statistical analysis plan
Scr, std	Serum creatinine measured with a standardized assay
SMD	Study medication diary
SOC	System organ class
SOF	Sofosbuvir
SOP	Standard operating procedure
sSAP	Supplemental statistical analysis plan
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post-treatment
SVR_8	Sustained virologic response 8 weeks post-treatment
SVR_{12}	Sustained virologic response 12 weeks post-treatment
SVR_{24}	Sustained virologic response 24 weeks post-treatment

Term	Definition
TD(q)	Target detected, quantifiable
TD(u)	Target detected, unquantifiable
TE	Treatment experienced
TF	Treatment failure
TN	Treatment naïve
TND	Target NOT detected (HCV RNA not detected)
TRD	Treatment-related discontinuation
TW	Treatment week
ULN	Upper limit of normal
US	United States (of America)
VEL	Velpatasvir
VL	Viral load

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	