THE LANCET HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV* 2015; published online July 10. http://dx.doi.org/10.1016/S2352-3018(15)00114-9.

Supplementary Materials

Efficacy and safety of grazoprevir and elbasvir in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): an open-label, noncomparative phase 3 trial

Jürgen K. Rockstroh, MD,[1] Mark Nelson,[2] Christine Katlama,[3] Jay Lalezari,[4] Josep Mallolas, MD, PhD,[5] Mark Bloch, MBBS,[6] Gail V Matthews,[7] Michael S. Saag,[8] Philippe J Zamor,[9] Chloe Orkin,[10] Jacqueline Gress,[11] Stephanie Klopfer,[11] Melissa Shaughnessy,[11] Janice Wahl,[11] Bach-Yen T. Nguyen, MD,[11] Eliav Barr, MD,[11] Heather L. Platt, MD,[11] Michael N. Robertson,[11] Professor Mark Sulkowski[12]

Liver biopsy staging in patients with cirrhosis

All patients were required to have liver disease staging by liver biopsy, Fibroscan (Echosens, Paris, France; cirrhosis defined as >12·5 kPa), or combination of Fibrotest score of >0·75 and an AST:platelet ratio index (APRI) of >2. Of the 35 patients (16·1%) with cirrhosis, 27 were diagnosed by Fibroscan, 6 by biopsy, and 2 by combination of Fibrotest and APRI.

HCV Sequence Analysis

Plasma samples from all subjects who participated in the study were collected prior to dosing to generate baseline sequence information. Additional samples were collected from subjects who met the criteria for virologic failure and follow-up visits whenever available. Due to assay limitations, only samples with viral titers above 1000 IU/mL were sequenced.

The HCV NS3 and NS5A regions from subject plasma samples were amplified using reverse transcription polymerase chain reaction (RT-PCR) followed by population sequencing. The limit of variant detection in the population was approximately 25% of the viral population.

Narratives of patients with serious AEs

Shortness of breath/pneumonia. A 58-year-old treatment-naive, black woman with HCV GT1a infection and cirrhosis was allocated to a regimen of grazoprevir (100 mg) and elbasvir (50 mg) on August 18, 2014. She developed symptoms of shortness of breath on September 23, 2014 and was initially treated with prednisone for an acute asthma exacerbation. Her symptoms worsened and she was admitted for pneumonia on September 28, 2014. She was started on moxifloxacin for community-acquired pneumonia and trimethoprim/sulfamethoxazole for possible PCP. She

continued on study medication throughout hospitalization and treatment of pneumonia. The patient completed TW12 and achieved SVR12.

Generalized convulsion. A 46-year-old white, treatment-naive, cirrhotic man with HCV GT4 infection and HIV co-infection was allocated to a regimen of grazoprevir (100 mg) plus elbasvir (50 mg) on July 21, 2014. On August 2, 2014, the patient experienced a witnessed generalized convulsion for approximately 5 minutes. It was reported that the patient fell onto a couch, was initially disoriented, and then had a generalized tonic-clonic convulsion associated with tongue biting. After approximately 5 minutes, the patient was oriented again. No preceding symptoms or signs were noted before the onset of the convulsion. The patient was admitted to hospital on August 2, 2014, where he was treated with levetiracetam. Laboratory findings were significant for an elevated CPK of 2148 U/L, but with no additional laboratory abnormalities noted during the hospitalization or follow-up. He underwent head CT, EEG, and brain MRI, all of which were grossly normal and subsequently recovered to baseline per clinical judgment. No discrete aetiology of the convulsion was found. The patient was discharged from the hospital August 14, 2014 and remains on levetiracetam 500 mg twice daily. He did not have any interruption of study medication. At TW4 (August 18, 2014), CPK had normalized to 108 U/L. INR was slightly elevated during treatment (range 1·1–1·4), likely related to underlying haemophilia and treatment. This patient completed TW12 on October 3, 2014 with no additional serious AE or further episodes of generalized convulsions and achieved SVR12.

Erysipelas. A 54-year-old white (not Hispanic or Latino), treatment-naive, non-cirrrhotic man with HCV GT1a infection and the *IL28B* CT genotype was allocated to a regimen of grazoprevir (100 mg) and elbasvir (50 mg) and received study medication from July 25, 2014 through October 20, 2014. He experienced erysipelas on January 9, 2015. The patient presented with a

painful, 4-cm area of induration behind the left knee associated with fever of 101°F on January 5, 2015, without any history of trauma. The patient was hospitalized for IV antibiotics. Symptoms and signs improved on January 12, 2015, and he was discharged on January 13, 2015. This serious AE was assessed by the PI to be not related to study medication. During the course of study medication, the patient also reported AEs of upper abdominal pain, somnolence, and constipation, all graded as mild and related to study drug. The subject's HCV declined to <15 IU/mL by day 7 and was subsequently TND from TW2 through the rest of the follow-up period and he achieved SVR12.

Acute psychosis and urinary retention. A 49-year-old white (not Hispanic or Latino), treatment-naive cirrhotic man with HCV GT4d infection was allocated on August 29, 2014 to grazoprevir (100 mg) plus elbasvir (50 mg) and completed his last dose on November 20, 2014. He experienced symptoms of acute psychosis on January 4, 2015, associated with urinary retention. The patient reported having abnormal feeling, hearing strange noises, feeling anxious and uncomfortable, and having disrupted sleep. He was hospitalised for 1 day on January 4, 2015, treated with alprazolam and olanzapine, and symptoms began to subside. At the same time, the patient also complained of hypogastric pain and urinary retention. A catheter was placed on January 4, 2015, and removed on January 7, 2015, after which the patient urinated spontaneously. However, the patient had a new episode of acute urine retention on January 17, 2015, and the catheter was again placed with the plan to keep it in place for 10–12 days. Both the acute psychosis and acute urinary retention were assessed to be not drug related. HCV RNA became TND at TW4 and the patient achieved SVR12.

Ulnar fracture. A 59-year-old black or African American (not Hispanic or Latino) treatment-naive, non-cirrhotic man with HCV GT 1a infection and *IL28B* CT genotype was allocated to

grazoprevir (100 mg) and elbasvir (50 mg) on July 16, 2014. He experienced a non-drug related serious AE of an ulnar fracture on November 24, 2014. The patient fell at home and presented to the ER where he was evaluated and diagnosed with an olecranon fracture. He was admitted for pain management and subsequently discharged home after the fracture was stabilised. The patient is following up with orthopedic surgery. Study medication was not interrupted. The patient has not reported any other AEs during the trial. HCV RNA became TND at TW6 and the patient achieved SVR12.

Spontaneous bacterial peritonitis. A 44-year-old white (not Hispanic or Latino) treatment-naive, cirrhotic man with HCV GT1b infection and *IL28B* CT genotype was allocated to grazoprevir (100 mg) and elbasvir (50 mg) and received study medication from August 22, 2014, through November 13, 2014. The patient was diagnosed with spontaneous bacterial peritonitis on January 17, 2015. He first noted edema in both lower extremities and ascites on January 17, 2015, and was admitted with a diagnosis of spontaneous bacterial peritonitis. He was treated with ceftriaxone, spironolactone, and furosemide. Recovery was observed and the patient was discharged on January 28, 2015, on norfloxacin, spironolactone, and furosemide. The principal investigator assessed this serious AE as not related to study medication. The patient achieved SVR12.

Narratives of patients with hepatic enzyme elevations

Elevation of ALT at TW2. This is a 46-year-old white man with HCV GT1a, and was non-cirrhotic, co-infected with HIV, and enrolled July 8, 2014. The patient had a history of a biliary stricture with biliary stent placement in 2009. At day 1, the patient's ALT and AST were 90 U/L

and 49 U/L. At TW2 (July 22, 2014), he was noted to have an ALT of 696 U/L (17× ULN), and an AST of 392 U/L (9× ULN), associated with slight elevation of direct bilirubin at 0·83 mg/dL. On July 23, 2014, the patient noted acute onset of nausea and pruritus. Urgent abdominal ultrasound showed dilated common bile duct and sludge in the right and left hepatic ducts. He was diagnosed with a biliary stent blockage on July 23, 2014, and underwent endoscopic intervention on July 24, 2014. Study drug therapy was interrupted for 3 days (July 26, 27, and 28, 2014). He resumed study drug with complete normalization of AST and bilirubin at week 4 and ALT and INR at TW6; these parameters remained normal through TW12. The patient completed TW12 on September 30, 2014. FW12 was completed on January 2, 2015, and SVR12 was achieved.

Elevation of ALT at TW6. 49-year-old white woman with HCV GT1a infection was non-cirrhotic, co-infected with HIV, and enrolled on July 10, 2014. At day 1, ALT, AST, alkaline phosphatase, bilirubin, and INR were all within normal limits and these parameters remained within normal limits until TW6 (August 22, 2014), when elevations in ALT to 136 U/L (4× ULN) and AST to 119 U/L (3× ULN) were noted. Bilirubin, alkaline phosphatase, and INR were normal. The site noted the patient was asymptomatic, with no new medications, and normal physical examination results. Therapy was continued. At TW8 (September 5, 2014), ALT increased further to 212 U/L, with INR elevated to a peak of 1·3, but a recheck 3 days later (September 8, 2014) showed ALT had declined to 162 U/L, and INR declined to 1·2. Abdominal ultrasound performed at the recheck visit on September 8, 2014 was normal. Further decline was noted at TW10 (September 19, 2014) with ALT of 51 U/L and INR normalized to 1·1. The patient remained asymptomatic throughout and other laboratory parameters (bilirubin, alkaline

phosphatase, and INR) have remained normal. The patient remained on study drug without any interruption. The patient completed TW12 on October 3, 2014, and FW12 was completed on December 29, 2014. SVR12 was achieved.

Elevation of AST at TW6. A 32-year-old black man with HCV GT1a infection was non-cirrhotic, co-infected with HIV, and enrolled on July 22, 2014. At day 1, his ALT and AST were 119 and 49 U/mL, respectively, and CPK was elevated to 447 U/L. At TW6 (September 3, 2014), the patient was noted to have an elevated CPK of 13 600 U/L associated with AST of 174 U/L (4·8× ULN). At that visit, the ALT was noted to be 104 (2·5× ULN, but not elevated greater than baseline), total bilirubin was elevated to 1·27 mg/dL, though direct bilirubin, alkaline phosphatase, and INR were all normal. Site was contacted for additional information and while the patient admitted to recent strenuous workouts, he was otherwise asymptomatic with a normal physical exam. Recheck of laboratory results 5 days later (September 8, 2014) showed reduction in CPK to 727 U/L, AST to 29 U/L, and ALT to 46 U/L. The investigator advised the patient to abstain from heavy workouts during the study period. TW8 laboratory results (September 16, 2014) showed continued decline in CPK to 379 U/L. AST, ALT, alkaline phosphatase, bilirubin, and INR were all within normal limits. The patient remained on study drug without any interruption. The patient completed TW12 on October 14, 2014 and FW12 was completed on January 12, 2015. SVR12 was achieved.

Elevation of ALT at TW10. A 58-year-old white man with HCV GT1b infection who was treatment naive and cirrhotic was enrolled on July 10, 2014, and on a regimen of grazoprevir (100 mg), elbasvir (50 mg) who at TW10 (September 18, 2014) had an ALT increase to 204 U/L

(5× ULN; BL=109), associated with AST increase to 180 U/L (4·2× ULN). Total bilirubin was slightly elevated to 1·13 mg/dL, and INR was 1·2. The site was contacted to get further information, and they reported that the patient was asymptomatic and denied any new medications or alcohol. Regular safety laboratory results at TW12 ([EOT] October 2, 2014) showed ALT had decreased to 134 U/L (3·35× ULN), and AST decreased to 69U/L (1·6× ULN). Total bilirubin increased slightly to 1·24 mg/dL, and INR increased to 1·8. The ALT combined with the INR met the criteria for a stopping rule; however, these laboratory values were from TW12 which was the end of treatment visit and medication was stopped per protocol. The patient completed TW12 on October 3, 2014, FW12 on December 22, 2014, and achieved SVR12.

Narratives of patients with transient HIV viremia

HIV breakthrough viremia. A 51-year-old woman co-infected with HCV GT 1a, non-cirrhotic, and previously on an ARV regimen of abacavir, lamivudine, and ritonavir-boosted atazanavir, and an additional dose of abacavir for the diagnosis of neurocognitive impairment. The ARV regimen was changed as of April 2014 to abacavir, lamivudine, and dolutegravir. The patient's HIV VL was TND at screening. Scheduled laboratory monitoring at day1 (July 8, 2014) revealed HIV viral load of 361 copies/mL. Repeat laboratory evaluation at TW4 revealed HIV viral load of 9638 copies/mL. No additional laboratory abnormalities were noted besides INR=1·2. The site was notified and provided additional compliance information. The patient had been erroneously taking an alternate ARV regimen consisting of dolutegravir 50 mg daily, abacavir 600 mg daily, and ritonavir 100 mg (for 6–8 weeks). The patient was educated and counseled regarding the appropriate ARV regimen of abacavir, lamivudine, and dolutegravir. The patient was continued in the trial without any missed study drug. Repeat laboratory results at TW8 and TW12 (October

7, 2014) revealed an undetectable HIV viral load. While the patient does meet criteria for HIV failure based on HIV viral load >200, measured at least 2 weeks apart, there is the concern that the suboptimal regimen explains the viral breakthrough.

HIV breakthrough viremia. A 43-year-old man co-infected with HCV GT 1a, non-cirrhotic and on an ARV regimen of abacavir, lamivudine, and raltegravir in June 2013. At screening on June 12, 2014, the HIV viral load was 180 copies/mL, recheck on June 26, 2014 showed HIV viral load ≤20 copies/mL, and at day1 on July 11, 2014, HIV viral load was undetectable. Routine laboratory evaluation at TW4 showed HIV viral load of 304 copies/mL. Repeat testing at TW8 showed HIV viral load of 3810. The site was contacted and provided additional history. The site reported that since 2009, the HIV viral load had fluctuated a bit, but had always been below 200 copies/mL. The site reported that while the patient took his medication every day, sometimes he took both raltegravir tablets at the same time, in order not to forget the second dose. The site performed additional education with the patient regarding the ARV regimen. Repeat evaluation showed HIV viral load of 30 copies/mL performed at the central laboratory, and 23 copies/mL performed at the local laboratory. This patient was compliant with the prescribed ARV, was continued on the same regimen, and was undetectable at follow-up testing.

Supplementary Table 1: Baseline resistance-associated variant (RAV) Summary by Treatment Response in GT1

Response Category	HCV Genotype	N	NS3 RAVs			NS5A RAVs			Both NS3 and NS5A RAVs		
			m	n	(%)	m	n	(%)	m	n	(%)
SVR12 Achieved	1a	136	134	66	(49·3)	135	8	(5·9)	134	6	(4·5)
	1b	42	42	5	(11·9)	42	5	(11·9)	42	0	(0·0)
	1-non-subtypable	1	0	0		0	0		0	0	
	Total	179	176	71	(40·3)	177	13	(7·3)	176	6	(3·4)
SVR12 Not Achieved	1a	5	5	3	(60·0)	5	2	(40·0)	5	2	(40·0)
	1b	1	1	0	(0·0)	1	0	(0·0)	1	0	(0·0)
	Total	6	6	3	(50·0)	6	2	(33·3)	6	2	(33·3)
Relapse	1a	5	5	3	(60·0)	5	2	(40·0)	5	2	(40·0)
	1b	1	1	0	(0·0)	1	0	(0·0)	1	0	(0·0)
	Total	6	6	3	(50·0)	6	2	(33·3)	6	2	(33·3)
Total	1a	141	139	69	(49·6)	140	10	(7·1)	139	8	(5·8)
	1b	43	43	5	(11·6)	43	5	(11·6)	43	0	(0·0)
	1non-sub-typable	1	0	0		0	0		0	0	
	Total	185	182	74	(40·7)	183	15	(8·2)	182	8	(4·4)

N=Number of subjects included in the analysis.

m=Number of subjects who had baseline samples sequenced for RAVs in the specified gene region.

n=Number of subjects who had specific RAV(s) detected at baseline. The following NS3 RAV(s) were selected for reporting: 036A, 036G, 036L, 036M, 036I, 054A, 054C, 054G, 054S, 055A, 055I, 056H, 080K, 080R, 107I, 122A, 122G, 122R, 132V, 155*, 156S, 156T, 156V, 156F, 156G, 158I, 168*, 170A, 170F, 170T, 170V, 175L. The following NS5A RAV(s) were selected for reporting: 028T, 028V, 028A, 030E, 030H, 030R, 030G, 030K, 030L, 030D, 031M, 031V, 031F, 058D, 093C, 093H, 093N, 093S. An asterisk (*) following a sequence position signifies that any variant (i.e. difference from the reference sequence) at that position is reported.

NS3 variants determined to have >5-fold resistance to GZR were included in the reporting: Y56H, R155G/T/W, A156G/T/V/L, D168A/G/T/V/L/I/F/Y/E/H/K/R.

NS5A variants determined to have >5-foled resistance to EBR were included in the reporting: M/L28T/A, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, 93C/H/N.

(%) = Percentage of subjects who had specific RAV(s) detected, calculated as (n/m)*100.

Supplementary Table 2: Baseline Resistance-Associated Variant (RAV) Summary by Treatment Response in GT 4 and 6

Response Category	HCV Genotype	N	NS3 RAVs			NS5A RAVs			Both NS3 and NS5A RAVs		
			m	n	(%)	m	n	(%)	m	n	(%)
SVR_{12} Achieved	4	27	27	3	(11.1)	27	11	(40.7)	27	3	(11.1)
	6	1	1	1	(100.0)	1	0	(0.0)	1	0	(0.0)
	Total	28	28	4	(14.3)	28	11	(39.3)	28	3	(10.7)
SVR_{12} Not Achieved	4	1	1	0	(0.0)	1	0	(0.0)	1	0	(0.0)
	Total	1	1	0	(0.0)	1	0	(0.0)	1	0	(0.0)
Relapse	4	1	1	0	(0.0)	1	0	(0.0)	1	0	(0.0)
	Total	1	1	0	(0.0)	1	0	(0.0)	1	0	(0.0)
Total	4	28	28	3	(10.7)	28	11	(39.3)	28	3	(10.7)
	6	1	1	1	(100.0)	1	0	(0.0)	1	0	(0.0)
	Total	29	29	4	(13.8)	29	11	(37.9)	29	3	(10.3)

N = Number of subjects included in the analysis.

m = Number of subjects who had baseline samples sequenced for RAVs in the specified gene region.

n = Number of subjects who had specific RAV(s) detected at baseline. The following NS3 RAV(s) were selected for reporting: 036*, 054*, 055*, 056*, 080*, 107*, 122*, 132*, 155*, 156*, 158*, 168*, 170*, 175*. The following NS5A RAV(s) were selected for reporting: 028*, 030*, 031*, 058*, 093*. An asterisk (*) following a sequence position signifies that any variant (i.e., difference from the reference sequence) at that position is reported.

(%) = Percentage of subjects who had specific RAV(s) detected, calculated as (n/m)*100.

Supplementary Table 3. Mean change from baseline in CD^{3+4+} cell count and CD^{3+4+} %

Visit Time Point	N	CD3+4+ count, cells/ µL Mean (SD, 95% CI))	CD3+4+ % Mean (SD, 95% CI)	Change From Baseline	
				Mean cell count (SD, 95% CI))	Mean CD %* (SD, 95% CI)
Baseline	218	618.82 (294.82,579.46 – 658.17)	31.22 (8.96, 30.02 - 32.41)	n/a	n/a
TW12	207	680.84 (323.96, 636.56 – 725.13)	31.30 (9.11, 30.05 - 32.54)	55.43 (160.74, 33.46 – 77.41)	-0.07 (3.44, -0.54 – 0.40)
FW12	212	653.44 (305.66, 612.16 – 694.73)	30.96 (8.81, 29.77 - 32.15)	33.74 (177.63, 9.75 – 57.73)	-0.21 (3.58, -0.70 – 0.27)

*change from baseline calculated for subjects with results at TW12 (n=208) and FW12 (n=213).

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P.O. Box 100
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TITLE:

A Phase III Open-Label Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naïve Subjects with Chronic HCV GT1, GT4, and GT6 Infection who are Co-Infected with HIV

IND NUMBER: 110,261
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
	Title	Subjects who are infected with HCV GT5 are no longer eligible for enrollment.
2.1	Trial Design	**Rationale:** Preliminary data from MK-5172 Protocol 047 demonstrated that 3 of the 4 HCV GT5 infected subjects treated with the two drug combination of MK-5172 + MK-8742 without ribavirin (the regimen being evaluated in the Phase 3 trials) experienced virologic failure. Even though these are very small numbers, we believe that these data indicate that this is not the optimal regimen for HCV GT5 infection.
4.2.2	Rationale for Dose Selection/Regimen/Historical Reference Rate	
5.1.1	Diagnosis/Condition for Entry into the Trial	
5.1.2	Subject Inclusion Criteria	
8.2.4.1	Efficacy Analysis Populations	
8.2.8	Subgroup Analyses and Effects of Baseline Factors	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
5.1.2	Subject Inclusion Criteria	Added language to document HCV RNA and HCV genotype must be confirmed by screening lab results. **Rationale:** To add clarity that these tests must be confirmed by screening lab results prior to a subject being enrolled/allocated to study medication.

Section Number (s)	Section Title(s)	Description of Change (s)
5.1.3	Subject Exclusion Criteria	Deletion of the text - "(lower limit of normal) of laboratory reference range" for serum albumin. **Rationale:** Incorrect text.
5.5	Concomitant Medications/Vaccinations (Allowed and Prohibited)	Addition of the allowed medications metformin and the Anti-coagulants: warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol. **Rationale:** To provide better clarity regarding which medications are allowed in the study. Addition of guidance stating that subjects taking P-gp substrates such as digoxin and colchicine should be monitored closely. **Rationale:** MK-5172A may have the potential to increase the exposures of P-gp substrates.
5.8	Subject Withdrawal/ Discontinuation Criteria	Revision of text regarding the INR results criteria for discontinuing a subject. **Rationale:** This change will prevent the inappropriate discontinuation of subjects who meet our entry criteria with a screening INR between 1.5 and 1.7 as well as the inappropriate discontinuation of subjects on anticoagulation.
5.10	Beginning and End of the Trial	Updated to include recently approved revised protocol template text. **Rationale:** To provide better clarity on what constitutes the end of the trial.
6.0	Trial Flow Chart	Addition of footnote explaining study medication is not dispensed at Visit 3 (Day 7). **Rationale:** To provide better clarity on when study medication is dispensed.
7.1.4.1	Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)	Addition of text – "All screening lab results must be reviewed and approved before a subject can be enrolled/allocated to study medication." **Rationale:** To ensure the PI and the sites are reviewing all laboratory results to make sure they meet the protocol specified criteria.

Section Number (s)	Section Title(s)	Description of Change (s)
9.5	Discard/Destruction/Returrns and Reconcilliation	Updated to include recently approved revised protocol template text. **Rationale:** To provide better clarity regarding the option for sites to locally discard and destroy clinical supplies.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-5172 in Combination with MK-8742 in Subjects with HCV/HIV Co-Infection.
Trial Phase	Phase III
Clinical Indication	Treatment of hepatitis C virus infection
Trial Type	Interventional
Type of control	No Active Control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
Number of trial subjects	Approximately 200 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 2 months of enrollment + 45 days (6.5 Weeks) for screening + up to an additional 36 weeks of treatment/follow-up for a total of 50.5 weeks from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for 42.5 weeks (maximum) from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 45 days or 6.5 weeks, each subject will be receiving assigned treatment for approximately 12 weeks. After the end of treatment each subject will be followed for 24 weeks for a total of up to 42.5 weeks in the study.
Randomization Ratio	N/A

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, multi-center, single-arm trial of 100 mg of MK-5172 in combination with 50 mg of MK-8742 (MK-5172A) in subjects with chronic HCV GT1, 4, or 6 infection, who are co-infected with HIV, to be conducted in conformance with Good Clinical Practices.

A total of 200 GT 1, 4, or 6 HCV infected, HIV-co-infected subjects will be enrolled. Approximately 20% of the enrolled subjects will have to have evidence of compensated cirrhosis at screening. All subjects must be HCV treatment naïve.

Study subjects will receive MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed.

Safety and tolerability will be carefully monitored throughout the study by the SPONSOR (or designee) in accordance with standard procedures.

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.

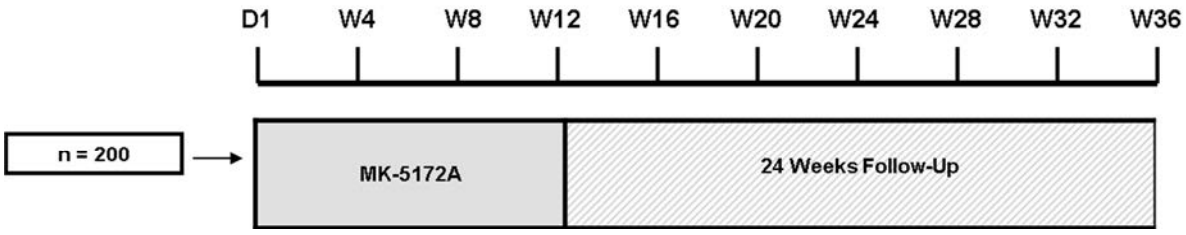

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving SVR12 (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.

   Hypothesis: The proportion of subjects receiving MK-5172 in combination with MK-8742 achieving SVR12 will be superior to 70%.

2) **Objective:** To evaluate the safety and tolerability of MK-5172 in combination with MK-8742.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving SVR24 (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA <LLOQ (either TD(u) or TND) 24 weeks after the end of all study therapy.

3.3 Other Objectives (e.g., Tertiary, Exploratory, etc.)

1) **Objective**: To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA <LLOQ at Weeks 2, 4, 12, and Follow-Up Week 4 (SVR 4).

2) **Objective:** To describe patient-reported outcomes related to health-related quality of life, fatigue, and work productivity/activity impairment before, during, and after treatment with MK-5172 and MK-8742.

3) **Objective:** To evaluate the emergence of viral resistance-associated variants (RAVs) to MK-5172 or MK-8742 when administered as part of a combination regimen.

4) **Objective:** To evaluate the pharmacokinetics (PK) of MK-5172 and MK-8742.

5) **Objective:** To explore the relationship between genetic variation and subject response to the treatment(s) administered.

6) **Objective:** To evaluate the proportion of subjects who develop HIV-1 virologic failure (HIV-1 RNA ≥ 200 copies/mL, confirmed on two consecutive tests at least 2 weeks apart, in subjects compliant with their HIV ARV therapies) during protocol therapy.

7) **Objective:** To evaluate the effect of the study regimen on CD4+ T-cell counts

4.0 BACKGROUND & RATIONALE

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5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with CHC genotype 1, 4, or 6 virus infection who are of 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. HCV RNA (≥ 10,000 IU/mL in peripheral blood) at the time of screening

3. have documented chronic HCV GT1, GT4, GT6 (with no evidence of non typeable or mixed genotype) infection:

    - Positive for anti-HCV antibody, HCV RNA, or any of the above HCV genotypes at least 6 months before screening (HCV RNA and HCV genotype must be confirmed by screening lab results), or

    - Positive for anti-HCV antibody or HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrollment with evidence of CHC disease, such as the presence of fibrosis)

4. have liver disease staging assessment as follows:

    Cirrhosis is defined as any one of the following [37, 38]:

- A liver biopsy performed prior to Day 1 of this study showing cirrhosis (F4)

- Fibroscan performed within 12 calendar months of Day 1 of this study showing cirrhosis with result >12.5 kPa [38]*

- A FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 and an aspartate aminotransferase (AST):platelet ratio index (APRI) of >2 . APRI formula: AST÷lab upper limit of normal (ULN) for AST x 100÷{platelet count÷100} (APRI calculation to be provided by the central laboratory.)

Absence of cirrhosis is defined as any one of the following:

- Liver biopsy performed within 24 months of Day 1 of this study showing absence of cirrhosis

- Fibroscan performed within 12 months of Day 1 of this study with a result of ≤12.5 kPa[38]*

- A FibroSure® (Fibrotest®) score of ≤0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) of ≤1 during Screening

*Fibroscan cut-off of 12.5 kPa has a positive predictive value of 90% and a sensitivity of 95% for ≥F3. Based on box and whisker plot of interquartile distribution >12.5 kPa will exclude the majority of subjects with metavir F3 fibrosis

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above critieria, a liver biopsy 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:

    - Treatment naïve: Naive to all anti-HCV treatment

      NOTE: Includes subjects who are treatment naïve who are ineligible to take IFN. See Section 7.1.2.1 for more details and definitions.

6. be HIV-1 infected, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Day 1) 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 viral load.

7. currently, are naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study) or be on HIV Antiretroviral Therapy (ART) for at least 8 weeks prior to study entry (Day 1) using a dual NRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS raltegravir [or dolutegravir or rilpivirine]. Dose modifications or changes in drugs during

the 4 weeks prior to study entry (Day 1) are not permitted. No changes in HIV regimen are allowed within 4 weeks of randomization. Subjects not on ART should have no plans to initiate therapy through at least Follow-up Week 4 of this study. Subjects on ART should plan to remain on the same therapy through at least Follow-up Week 4 of this study.

8. CD4+ T-cell count > 200 cells/mm^3 at screening (for subjects currently on stable ART); CD4+ T-cell count >500 cells/mm^3 at screening (for subjects who are naïve to treatment with ART).

9. have documented undetectable plasma HIV-1 RNA at screening and at least 8 weeks prior to screening. For subjects not on ART, HIV RNA must be <50,000 copies/mL.

10. have at least one viable antiretroviral regimen alternative beyond their current regimen in the event of HIV virologic failure and the development of anti-retroviral drug resistance.

11. agree to the following:

    - 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.

    - The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence† from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡:

      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

12. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

13. provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

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. For cirrhotics, subjects that are Child-Pugh Class B or C or who have a Pugh-Turcotte (CPT) score >6, must be excluded.

   NOTE : To calculate the Child-Pugh score, refer to the following website: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality.

3. is coinfected with hepatitis B virus (e.g. HBsAg positive).

4. 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.

5. 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 of Day 1 not available, imaging is required during screening.

6. is taking or plans to take (a) any HIV therapy that includes a ritonavir-boosted or un-boosted protease inhibitor, efavirenz or etravirine; (b) any other prohibited medications listed in Section 5 of this protocol; or (c) herbal supplements, including but not limited to St. John's Wort (Hypericum perforatum) within 2 weeks of Day 1.

7. 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.

8. has a clinically-relevant drug or alcohol abuse within 12 months of screening

9. is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from Day 1 and continue throughout treatment, and 14 days after the last dose of study medication, or longer if dictated by local regulations.

10. has any of the following conditions:

    - Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.
    - Poor venous access that precludes routine peripheral blood sampling required for this trial.
    - Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).
    - History of a medical/surgical condition that resulted in hospitalization within the 3 months prior to enrollment, other than for minor elective procedures
    - Medical/surgical conditions that may result in a need for hospitalization during the period of the study
    - Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, TNF antagonists, or other immunosuppressant drugs during the course of the trial

11. has any condition or prestudy laboratory abnormality, ECG abnormality or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.

12. had a life-threatening SAE during the screening period.

13. For subjects with HIV, history of opportunistic infection in the preceding 6 months prior to screening. A list of these events may be found in Appendix B of the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

14. For subjects with HIV, use of HIV drugs other than a dual NRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS raltegravir [or dolutegravir or rilpivirine]

15. has evidence or history of chronic hepatitis not caused by HCV, including but not limited to nonalcoholic steatohepatitis (NASH), drug-induced hepatitis, and autoimmune hepatitis.

    NOTE: Subjects with history of acute non-HCV-related hepatitis, which resolved >6 months before study entry (Day 1), can be enrolled.

16. has exclusionary laboratory values as listed below:

    NOTE: If any of the laboratory exclusion criteria below in Table 3 are met, the site may have the abnormal value retested one time.

Table 3 Laboratory Exclusion Criteria

Laboratory Assessment	Subject Population Noncirrhotic/Cirrhotic Subjects
Creatinine Clearance	<50mL/min
hemoglobin	< 9.5 g/dL for both male and female subjects
platelets	<50 x 10^3/µL
Serum Albumin	< 3.0 g/dL
INR	>1.7, unless subject has a stable INR on an anticoagulant regimen.
HbA1c	>10%
ALT	>10XULN
AST	>10XULN

17. 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(s) to be used in this trial are outlined below in Table 4.

Table 4 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-5172A (fixed dose combination of MK-5172 and MK-8742)	100 mg/50 mg	QD	Oral	12 Weeks	experimental

The first dose of trial treatment will be administered at the trial site at Visit 2 (Day 1). 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 (Escalation/Titration/Other)

Dose modification of MK-5172A is **not** permitted.

5.2.2 Timing of Dose Administration

Subjects will be instructed to take MK-5172A without regard to food.

If a subject misses a dose of MK-5172A 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 for any reason MK-5172A needs to be interrupted it can be interrupted for up to 3 days. If MK-5172A is interrupted for more than 3 days, consult the Sponsor Protocol team.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

As this is a single arm study where all subjects will receive the same treatment regimen, no randomization is required. The interactive voice response system / integrated web response system (IVRS/IWRS) will dispense study drug.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the dosing period. If there is a clinical indication for any medication or vaccination specifically prohibited during the dosing period, 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.

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.

- At each visit, subjects should be questioned about any new drug they are taking.
- 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.
- Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

The following medications/therapies are contraindicated during the dosing period:

Known hepatotoxic drugs, including but not limited to:

- Etofoxine
- Isoniazid
- Nitrofurantoin
- Phenytoin

Herbal supplements

Strong and moderate CYP3A/P-gp inducers, including but not limited to:

- Anti-infectives: nafcillin, rifampin
- Anticonvulsants: carbamazepine, phenytoin, phenobarbital
- bosentan
- modafinil
- St. John's Wort

OATP inhibitors, including but not limited to:

- Immunosuppressants: cyclosporine
- Anti-infectives: rifampin
- gemfibrozil
- eltrombopag
- lapatinib

HIV medications, including but not limited to:

- efavirenz
- etravirine
- all ritonavir-boosted and unboosted HIV protease inhibitors

HMG-CoA reductase inhibitors (statins):

- simvastatin
- fluvastatin
- rosuvastatin greater than 10 mg (see Allowed Medications, below)
- atorvastatin greater than 10 mg (see Allowed Medications, below)

In general, CYP3A4 substrates with narrow therapeutic ranges (e.g. alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, terfenadine) are not prohibited, but their levels have the potential to be increased by approximately 30%. Therefore, subjects taking these medications should be monitored closely or dose adjusted appropriately.

In general, P-gp 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.

Investigational agents are not permitted.

Systemic corticosteroids (dose equivalent to ≥ 10 mg prednisone per day, except in the case of rapid steroid tapers <1 week in duration) are not permitted.

Allowed Medications:

The following concomitant medications are allowed in this study:

Anticoagulants: warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol

Antihypertensives:

- ACE inhibitors/ARB: 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: verapamil, diltiazem, amlodipine
  Note: for other calcium-channel blockers, please consult with the Sponsor
- hydralazine, clonidine, minoxidil, isosorbide nitrates

Anemia: erythropoetin

Diuretics: HCTZ, furosemide, spironolactone, triamterene

Hypoglycemic agents: insulin, metformin, sitagliptin, glipizide

Contraceptives: oral contraceptive pills, progesterone injects, intrauterine devices

Antidepressants/anxiolytics: citalopram, paroxetine, duloxetine, escitalopram, fluoxetine, bupropion, trazodone, diazepam, clonazepam, temazepam, lorazepam

Acid reflux: H2 blockers, proton pump inhibitors

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: use the lowest possible effective dose of atorvastatin, but do not exceed a daily dose of 10 mg

Concomitant medications and therapies discontinued during the dosing period may be restarted 2 weeks after the last dose of study drug is administered and may continue during the follow-up period.

Note: For other medications not listed here, please consult with the Sponsor.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

MK-5172A can be taken without regard to food.

Considerations for Study Visits
Procedures visits should be scheduled as close to the indicated study days and study weeks as possible. See the Study Flow Chart in Section 6 for a complete listing of study procedures required at each visit. Collection of PK samples (predose and/or postdose) must be taken as indicated in Table 6 in Section 7.1.4.2.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- 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.

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

- Subject meets any HCV virologic failure criteria (see Section 4.2.3.1.1.2)
- Subject becomes pregnant during the trial.

- A physician investigator feels it is in the best interest of the subject to discontinue.
- The subject's ALT or AST increases to >500 IU/L.
- The subject's ALT or AST increases to >3x baseline, is >100 IU/L, 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)
- The subject's ALT or AST increases to >3x the nadir value, is >100 IU/L, 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).
- The subject's ALT or AST increases to >3x baseline, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following adverse events that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to MK-5172: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).
- The subject's ALT or AST increases to >3x the nadir value, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following adverse events that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to MK-5172: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).
- The subject's alkaline phosphatase increases to >3x ULN, a simultaneous increase in total bilirubin > 2x ULN and other causes of elevated alkaline phosphatase are excluded.
- The subject's alkaline phosphatase increases to >5x ULN and other causes of elevated alkaline phosphatase are excluded.

A subject **may** be discontinued from treatment for any of the following reasons:

- 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.
- Failure to comply with the dosing, evaluations, or other requirements of the trial

Clinical management of HIV-1 virologic failure will be handled by site investigators according to current HIV treatment guidelines and local standard of care. Patients with HIV virologic failure may continue in the study unless there is a requirement for prohibited concomitant medications (see section 5.4) to construct a new HIV treatment.

5.9 Subject Replacement Strategy

A subject who discontinues 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, discontinues 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

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Study Flow Chart

Study Period (12 Week)	Scr	1st Week		Treatment Weeks						Follow-Up Weeks						Unscheduled	
		Day 1[10]	Day 7	2	4	6	8	10	12	FU 4	FU 8	FU 12	FU 16[13]	FU 20[13]	FU 24	Unsched/HIV/HCV Viral Fail Conf Visit	Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Visit Window	NA	NA	-1 to +14days							-1 to +3 week						NA	NA
ADMINISTRATIVE PROCEDURES																	
Informed Consent	x																
Informed Consent for Future Biomedical Research	x																
Inclusion/Exclusion Criteria	x																
Subject Identification Card	x																
Medical History	x																
Prior and Con-med Review	x	x	x	x	x	x	x	x	x							x	x
Treatment Allocation/Randomization		x															
Review Study Medication Diary		x	x	x	x	x	x	x	x								x
CLINICAL SAFETY EVALUATIONS																	
Physical Examination[1]	x	x					X[1]		x[1]								x
Weight	x	x															x
Height	x																
12-Lead ECG	x								x								x
Vital Signs	x	x			x		x		x	x							x
Subject confirmation of birth control	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x
Review (Serious) Adverse Events[2]	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x
Telephone contact													x	x			
PATIENT REPORTED OUTCOME[3]																	
SF-36v2® Health Survey Acute		x			x				x			x			x		x
EQ-5D-5L		x			x				x			x			x		x
FACIT-Fatigue Scale		x			x				x			x			x		x
Work Productivity & Activity Impairment (WPAI): Hepatitis C		x			x				x			X			x		x
Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV) [Administered to subjects in United States only]		x			x				x			x			x		x
LABORATORY SAFETY EVALUATIONS																	
Coagulation	x	x	x	x	x	x	x	x	x							x	x
Chemistry & Hematology	x	x	x	x	x	x	x	x	x	x	x	x				x	x
HBA1C	x																
HBsAg	x																
HIV-1 Serology	x																

Study Period (12 Week)	Scr	1st Week		Treatment Weeks						Follow-Up Weeks						Unscheduled	
		Day 1[10]	Day 7	2	4	6	8	10	12	FU 4	FU 8	FU 12	FU 16[13]	FU 20[13]	FU 24	Unsched/HIV/HCV Viral Fail Conf Visit	Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Visit Window	NA	NA	-1 to +14days							-1 to +3 week						NA	NA
Urinalysis		x			x		x		x	x						x	x
Urine Pregnancy Test (females of child bearing potential only)[4]	x	x			x		x		x	x	x	x			x	x	x
PHARMACOKINETICS																	
MK-5172 PK		x		x	x		x		x								x
MK-8742 PK		x		x	x		x		x								x
Meal information for PK		x		x	x		x		x								x
HCV EVALUATIONS																	
HCV Genotype Determination	x																
Liver imaging[5]	x																
HCV RNA Level[8]	x	x	x	x	x	x	x	x	x	x	x	x			x	x	X[11]
Plasma for HCV Viral Resistance and Biomarker[6, 8]		x								x	x	x			x	x	X[11]
Blood (DNA) for genetic analysis[7]		x															
HIV EVALUATIONS																	
HIV RNA	x	x			x		x		x	x	x	x			x		x
Plasma for HIV Viral Resistance[9]		x														X[9]	x
CD4+ T-cell counts	x	x			x		x		x	x	x	x			x		x
DRUG ADMINISTRATION																	
MK-5172A (Fixed Dose Combination 100 mg MK-5172/50 mg MK-8742, open label)		x	X[14]	x	x	x	x	x	x[12]								

[1] A comprehensive PE will be done at screening and baseline (Day1). For all other visits a focused PE will be conducted when clinically indicated.

[2] Review of Adverse Events should include collecting serious adverse events throughout the study and collecting all adverse events Day 1 (post-dose) through 14 days following the last dose of study drug. Adverse events occurring prior to study drug administration or after study drug discontinuation, as a result of a protocol-specified procedure or intervention, should also be reported.

[3] Patient Reported Outcomes will be done only on Day 1, WK4, WK12 (end of therapy visit), FU 12, FU 24, and early discontinuation visits for all subjects. There are a total of five questionnaires in the study (the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, the WPAI: Hepatitis C and the CLDQ-HCV). Only at sites in the United States (US), subjects, whose native language is either English or Spanish, will be eligible to complete all five questionnaires, including the CLDQ-HCV. At all other sites outside the US, subjects will be eligible to complete the questionnaires only if language translations are available in the subject's native language for all four of these questionnaires: the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, and the WPAI: Hepatitis C. The questionnaires will be administered in the following sequential order: the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, the WPAI: Hepatitis C and the CLDQ-HCV.

[4] Serum pregnancy testing will only be performed to confirm a positive urine pregnancy test. When study visits are spaced more than one 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 post dosing. 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.

[5] For cirrhotic subjects only, an ultrasound of the liver (not a fibroscan) should be performed within 4 weeks prior to randomization to rule out hepatocellular carcinoma. If a subject already had a CT scan or an MRI scan within 6 months of randomization, readings from these imaging techniques are also acceptable.

[6] Blood samples will be collected for HCV viral resistance testing at baseline, viral failure confirmation visit, and FU4, FU8, FU12, and FU24 visits. At the same time points, samples will be collected for proteomics, and metabolomics and other exploratory analysis.

[7] Blood sample will be collected for IL28 and genetic analysis. Any leftover extracted DNA will be stored for future biomedical research if the subject provides consent. Testing will be limited to IL28 if there is a documented law or regulation prohibiting genetic analysis.

[8] Any leftover plasma from HCV RNA, leftover plasma for HCV viral resistance and biomarker will be stored for future research if the subject consents to participate in the FBR sub-study.

[9] Blood samples will be collected for HIV viral resistance at baseline and at the time of HIV RNA failure confirmation, the sample will be shipped to the referral laboratory.

[10] Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.

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

[12] There will be no dispensing of study medication on this day for subjects receiving 12 weeks of therapy. However, the subject will take their last dose(s) of week 12 on that day.

[13] FU16 and FU20 visits are virtual visits. The study nurse will have telephone contact with the subject to make sure that he/she is doing well and as a reminder for FU 24 visit.

[14] Drug is not dispensed via IVRS at this visit

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.

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.

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

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 during 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 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 7.1.5.4 and 7.1.6.1.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after treatment allocation. Once a 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 randomization number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

The investigator/study coordinator will give the subject an electronic Study Medication Diary (eSMD) to be completed during the study period. The investigator/study coordinator will be responsible for entering the subject's identification (allocation number), and other pertinent subject information before giving the eSMD to the subject. The subject will be instructed to record dates/times and the number of tablets or capsules of study drug doses on the eSMD for the entire time period. Only the subject should enter information into the eSMD. The subject is to return the eSMD for inspection at each scheduled visit and is to return the eSMD to the investigator/study coordinator at the end of the treatment period. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the eSMD by comparing entries with amounts of returned study medication. 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 eSMD. The investigator/study coordinator will be responsible for reconciling the appropriate information from the eSMD into the appropriate case report form.

Interruptions from the protocol specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Assessment of IFN Treatment Eligibility Status

This study will enroll a treatment-naïve population, which included subjects who are ineligible to receive INF based therapy. As described in Section 8.2.5.3, a subgroup analysis will be performed to assess the consistency of the response across IFN eligible and ineligible subjects. Therefore, the investigator will assess if the subject meets any of the following criteria for being ineligible to receive IFN based therapy.

- IFN ineligible: Subject is treatment naïve and deemed ineligible by the investigator for treatment with IFN due to at least one of the following co-morbidities that is deemed at risk for worsening with IFN treatment (one of these comorbidities must be recorded on the Medical History eCRF):

    - Autoimmune disorders including but not limited to: dermatomyositis, immune (idiopathic) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus

    - Significant psychiatric disease necessitating hospitalization or period of disability

    - or a history of psychosis, schizophrenia, bipolar disorder, moderate depression,

    - schizoaffective disorder, suicidal ideation, or suicide attempt

    - Seizure disorder

    - Poorly controlled thyroid dysfunction; hyperthyroidism (TSH $\geq$ 2 x the upper limit of normal (ULN) and $\leq$ 10 x ULN) or hypothyroidism (TSH < the lower limit of normal (LLN) and > 0.1 μIU/mL)

    - Retinal disease

    - Poorly controlled diabetes (HbA1c > 6.1% and $\leq$ 10%)

7.1.2.2 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 and Day 1 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 exams should be performed when clinically indicated. For all other visits, a focused exam will be performed when clinically indicated. Any significant changes between the screening visit and Day 1 should be noted in the Medical History eCRF. Any significant changes after receiving study therapy at Day 1 must be reported as adverse events and entered on the adverse event eCRF. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

7.1.2.3 Weight and Height Assessment

The subject's weight should be assessed as mentioned in the flow chart. Clinically significant changes from Day 1 should also be captured as AEs in the CRF.

7.1.2.4 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.

7.1.2.5 Vital Signs

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

Note: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, and axillary temps may be taken.

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

7.1.2.6 Birth Control Confirmation

Confirmation must be obtained by site personnel that subjects and their partner(s) are using acceptable methods of contraception. This assessment must be documented in the subject's study chart at each specified visit.

7.1.2.7 Adverse Events

The principal investigator or sub-investigator (physician, physician assistant or nurse practitioner) must determine the severity and relationship to study medication(s) of all adverse events. A physician investigator must review, initial and date the severity of all adverse events and their relationship to study medications when initial assessment of an adverse event is made by a physician assistant or nurse practitioner. Designated medical practitioners must be licensed and the responsibilities transferred to them must be documented in the site file. For details please refer to Section 7.2.

7.1.2.8 Noninvasive Methods of Cirrhosis Evaluation

FibroScan - This method for assessing liver cirrhosis has gained increasing acceptance. In the US, this methodology is 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 or 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 [39], a population of patients with

chronic hepatitis C, a cut-off of 12.5 kPa was selected for cirrhotics. At this cut-off, 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 patients with chronic hepatitis C, the cut-off value ≤ 12.5 kPa used by Castera was selected to exclude 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 hepatitis C infections. One such algorithm, the Sequential Algorithm for Fibrosis Evaluation (SAFE), which uses a combination of Fibrotest and the aspartate aminotransferase-to platelet ratio index (APRI) is very accurate for diagnosing cirrhosis [40]. 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 cut-off values for excluding cirrhotics using the two 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 and that 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. Accordingly, the Sponsor is confident these cut-off values that will differentiate cirrhotic from non-cirrhotic patients with reasonable accuracy in this study.

7.1.3 Patient-Reported Outcomes

There are a total of five questionnaires in the study: SF-36v2® Health Survey Acute, EuroQol EQ-5D-5L, FACIT-Fatigue Scale, WPAI: Hepatitis C and the CLDQ-HCV. The CLDQ-HCV will only be administered to subjects in the United States.

SF-36v2® Health Survey Acute

The SF-36v2® Health Survey, Acute (1-week recall) Form, is a generic health survey which includes 36 questions to measure functional health and well-being from the subject's perspective. The acute, 1-week recall version of the form was selected to detect more recent changes in health status. The SF-36v2® measures each of the following eight health domains: Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health. The eight health domain scores contribute to the computation of the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The SF-36 has been used extensively in several HCV-infected populations and clinical trials for the treatment of HCV infection [30, 31,32,33,34,35,36].

EQ-5D-5L

The EuroQol EQ-5D-5L is a validated, standardized 5-item health-state questionnaire applicable to a wide range of health conditions and treatments and used to assess health outcomes [41, 42, 43]. The five health state dimensions include: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The recall period is today. The EuroQol EQ-5D-5L also includes a graded (0 to 100) 20 centimeter vertical visual analog scale (EQ VAS) on which subjects rate their current general state of health, from 'the worst health you can imagine' to 'the best health you can imagine'. The EuroQol EQ-5D-5L provides a simple descriptive profile and a single index value for health status that can be used to develop health utilities or "quality adjusted life years" for health economic analyses. The EQ-5D-5L has been used in HCV-infected populations.

FACIT-Fatigue Scale

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale), Version 4, is a 13-item questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function (e.g, trouble doing things, need to sleep, and social limitations). The FACIT-Fatigue Scale uses a 5-point Likert-type response scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much) with a recall period of "during the past 7 days." The FACIT-Fatigue Scale has been found to be reliable and valid in patients with fatigue [44]. The FACIT-Fatigue Scale has been used in HCV-infected populations

WPAI: Hepatitis C

The Work Productivity and Activity Impairment Questionnaire, Hepatitis C (V2.0) (WPAI: Hepatitis) is a self-administered questionnaire which evaluates the effect of hepatitis C on the subject's ability to work and perform regular activities [49]. The WPAI: Hepatitis C consists of six items including questions about the subject's work and daily activities. The recall period for this questionnaire is 7 days. The WPAI: Hepatitis C has been used in HCV-infected populations.

CLDQ-HCV [Administered to subjects in the United States only]

A HCV-specific version of the Chronic Liver Disease Questionnaire (CLDQ-HCV) measures disease-specific HRQOL. The CLDQ-HCV has been tested in several HCV-positive populations and is reliable and valid for longitudinal change over time [45, 46, 47, 48]. The CLDQ-HCV consists of 29 questions divided into 4 domains: activity and energy (AE), emotional (EM), worry (WO), and systemic (SY). The CLDQ-HCV has a 7-point Likert-type response scale ranging from 1(most impairment) to 7 (least impairment) and a recall period of "during the last two weeks". The CLDQ-HCV has been used extensively in HCV-infected populations.

Administration

Subjects are to complete the questionnaires on their own at the site using an electronic data capture tool at the beginning of the appropriate study visit (see study flow chart). Every attempt should be made for the subjects to complete the questionnaires prior to receiving study treatment, discussing any medical conditions with the study personnel, or receiving any

medical results. Only at sites in the United States (US), subjects, whose native language is either English or Spanish, will be eligible to complete all five questionnaires: the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, WPAI: Hepatitis C and the CLDQ-HCV. At all other sites outside the US, subjects will be eligible to complete the questionnaires only if language translations are available in the subject's native language for all four of these questionnaires: the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, and the WPAI: Hepatitis C. The questionnaires will be administered in the following sequential order: the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, the WPAI: Hepatitis C and the CLDQ-HCV. Questionnaires will not be administered to subjects if native language translations are not available for all questionnaires. Together, these questionnaires should take each subject approximately 20-30 minutes to complete the SF-36v2®, EQ-5D-5L, FACIT-Fatigue Scale, and the WPAI: Hepatitis C and an additional 10 minutes to complete the CLDQ-HCV.

7.1.4 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. 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 12.4.

7.1.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5. All screening lab results must be reviewed and approved before a subject can be enrolled/allocated to study medication.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Bilirubin	Hemoglobin A1C (HbA1c)
Hemoglobin	Alkaline phosphatase	Blood	Hepatitis C Virus Genotype
Platelet count	Alanine aminotransferase (ALT)	Glucose	HBsAg (screening only)
WBC (total and differential)	Aspartate aminotransferase (AST)	Ketone	HIV-1 serology (screening only)
Erythrocytes (RBC count)	Creatinine	Leukocyte Esterase	Prothrombin time (PT)
	Creatinine Clearance (screening only)	Nitrite	International normalized Ratio (INR)
	Creatine Kinase	pH	Choriogonadotropin Beta (Urine pregnancy test kits to sites)
	Gamma-glutamyltransferase	Protein	CD4 + T-cell count
	Glucose (serum glucose)	Specific Gravity	Plasma HIV-1 RNA
	Amylase	Bacteria	Plasma HCV RNA
	Lipase	Squamous Epithelial Cells	Fibrosure® (Fibrotest) as requested by site for entry criteria (may be performed locally)
	Potassium	RBC	APRI calculation (screening only)
	Sodium	WBC	Coagulation
	Total Bilirubin		
	Direct Bilirubin		
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

7.1.4.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics 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 pharmacodynamic markers.

7.1.4.2.1 Blood Collection for Plasma MK-5172 and MK-8742

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

All subjects allocated and enrolled in the study will be part of the population PK group (i.e. sparse PK sampling scheme). See Table 6 for sampling scheme. On all PK visits where

predose sample will be collected, subject must withhold their dose on the day of the PK visit; the dose will be administered at the site after collection of the predose PK sample.

All PK samples will be used to evaluate not only PK exposures but also to assess the PK/PD and PK/AE relationships of MK-5172 and MK-8742, as appropriate. The date and time of each PK sample as well as the date and time of the last dose of MK-5172A prior to the PK sample will be recorded. In addition to PK sample collection, information regarding meal time and qualitative fat content of the meal consumed prior to dose of MK-5172A (last dose prior to the PK sample) will be gathered for days where PK samples are collected.

Information regarding qualitative fat content in meals can be found in Appendix 12.6.

Table 6 Pharmacokinetic Sampling Timepoints – Population PK (All Subjects)

Visit Number	Study Day/Week	Time Relative to Dose of MK-5172A[2]	MK-5172 PK Sample[1]	MK-8742 PK Sample[1]
2	Day 1	Predose	x	x
4	Week 2	Predose	x	x
5	Week 4	Anytime	x	x
7	Week 8	2 hrs Postdose	x	x
9	Week 12	Predose	x	x
17	Early Discon Visit	NA[2]	x	x

[1] ~4 mL of blood will be collected at each specified time point for plasma PK assessments of MK-5172
~4 mL of blood will be collected at each specified time point for plasma PK assessment of MK-8742
[2] Time Relative to last Dose of MK-5172A must be recorded in INFORM
Note: The date and time of the PK sample collection for all MK-5172, MK-8742 PK samples must be recorded in INFORM
Note: At the time of PK sample collection, subjects will be asked to provide information regarding the time/date of the last MK-5172A dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary).

7.1.4.3 Future Biomedical Research

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

- Leftover DNA for future use
- Leftover plasma from HCV RNA
- Leftover plasma from viral resistance and biomarkers

7.1.4.4 HCV Evaluation

The following specimens are to be obtained as part of Efficacy/Pharmacogenetic Measurements:

- Samples for HCV Genotype evaluation must be obtained for inclusion in the study.
- Blood must be drawn from each subject to assess HCV RNA plasma levels at various time points as shown in the flow chart. HCV-RNA in plasma will be measured using the Roche COBAS® AmpliPrep/COBAS® Taqman™ HCV Test, v2.0 assay with a

lower limit of quantification (LLOQ). Leftover plasma may be used for future biomedical research only if the subject signed for future biomedical 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 future biomedical research only if the subject signed for future biomedical 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 (sustained viral response).

- Samples collected for genetic analysis are obtained at Day 1. Any leftover DNA may be used for future biomedical research only if the subject signed for future biomedical consent.

Note: Samples may also be used for future assay development and validation

7.1.4.5 HIV Evaluation

The following specimens are to be obtained:

- Blood must be drawn from each subject to assess HIV RNA plasma levels at various time points as shown in the study flow chart (Section 6). HIV-RNA in plasma will be measured using a COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 assay with a lower limit of quantification of <20 IU/mL.

- Blood must be drawn from each subject at HIV RNA viral failure confirmation visit (in case of potential failure, 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) to assess viral resistance mutations, and processed as instructed by the central laboratory manual. HIV-1 drug resistance will be assessed using the PhenoSense GT™ HIV Assay and the Genosure Prime Assay.

- Blood must be drawn from each subject to assess immunologic status. CD4+ T-cell counts will be obtained at screening and at various time points as shown in the flow chart.

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

- HIV-1 RNA <LLOQ, Target Not Detected
- HIV-1 RNA <LLOQ, Target Detected
- HIV-1 RNA copies/mL

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from 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.

7.1.5.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. 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), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction cannot be processed.

7.1.5.2 Blinding/Unblinding

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

7.1.5.3 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 with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

7.1.5.4 Rescreening

- Subjects who have previously completed the screening visit (Visit 1) and were deemed eligible for randomization into this study, but failed to be randomized 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

- HBsAg

- HIV-1 serology

- Liver biopsy/Fibroscan/ FibroSure® (Fibrotest®)

- Liver Ultrasound

- 12-Lead ECG

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

7.1.5.5 PK Sampling Time Points

Subjects must follow the protocol defined specific time points for predose or post dose in respect to study medication administration for PK sample collection. If predose PK sample is required by the protocol, the subject should withhold their dose the day of PK sample. For detailed time points of PK sample collection please refer to Table 6 in Section 7.1.4.2.1.

7.1.6 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.

7.1.6.1 Screening

Approximately 45 days prior to randomization, 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 Inclusion Criteria Section 5.1.2) from at least 2 weeks prior to Day 1, throughout treatment, and 14 days 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 Study Flow Chart must be completed and subject eligibility confirmed by the investigator prior to the subject's randomization and drug administration.

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

7.1.6.2 Treatment Period

Treatment Day 1 (Visit 2)

Pretreatment Procedures

Day 1 procedures listed on the Study Flow Chart should be performed prior to dosing unless specified otherwise. For female subjects, 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 randomization and the remainder of the pretreatment (Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, the subject must not be randomized.

Blood will be collected for assay of safety evaluations, plasma HCV RNA, HIV RNA, 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-5172 and MK-8742 therapies.

7.1.6.3 Drug Administration

Following completion of the Day 1 procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS for assignment of the drug to be administered. 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.

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, collect the following information when a subject discontinues:

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

7.1.6.4 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. If a subject completes 12 weeks of therapy, the 4, 8, 12, and 24–week follow-up visits will occur approximately 16, 20, 24, and 36 weeks after Day 1, respectively. Follow up visits at 16 and 20 weeks after the last dose of study drug, will be virtual visit, 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 24 visit.

Subjects who discontinue because they have met criteria for HCV virologic failure while on study therapy should complete an Early Discontinuation Visit as outlined in the Study Flow Chart (Section 6), and return to the study site for follow-up visits at 4, 8, 12, and 24 weeks following the confirmation of HCV virologic failure. Subjects who meet the HCV virologic failure criterion of relapse (having HCV RNA $\geq$ LLOQ following end of all study therapy, after becoming undetectable (TND) at end of treatment) will return to the study site for follow-up visits at 4, 8, 12, and 24 weeks as outlined in the Study Flow Chart (Section 6).

Subjects who discontinue for reasons other than HCV virologic failure should complete an Early Discontinuation Visit as outlined in the Study Flow Chart and return to the study site for follow-up visits at 4, 8, 12, and 24 weeks following the discontinuation of treatment.

Follow-up after Trial Completion

All subjects who have taken at least one dose of MK-5172 or MK-8742 will be asked to consent to a follow-up protocol (MK-5172 Protocol 017, a 3 year follow-up program to study efficacy and/or resistance associated variants to any compound used in a MK-5172 treatment regimen). Subjects included in this follow-up protocol may include subjects who have initiated other HCV treatments i.e. rescue or other clinical trials, subjects who failed therapy in this trial who do not want to initiate a new HCV treatment and subjects who achieved viral remission during this trial. The purpose of this follow-up protocol is to follow resistance

associated variants (RAVs) over time and in the case of treatment responders, to follow durability of response.

7.1.6.5 Evaluation of Laboratory Safety Signals

Laboratory safety measurements will be evaluated weekly throughout the study to assess potential liver safety signals.

If a subject has one or more of the laboratory ECI criteria (Refer section 7.2.3.2) at the last dosing visit (Week 12), 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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 14 days following cessation of treatment and 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.

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 higher than: Any intake in excess of the prescribed dose of MK-5172 or MK-8742 per calendar 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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) that occurs during the trial or within 14 days of completing the trial. All subjects who become pregnant 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. Sponsor Contact information 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 a cancer;

- Is associated with an overdose;
- Is an other important medical event

Refer to Table 7 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 and not associated with virologic failure.*

3. first instance of ALT or AST >3x baseline AND >100 IU/L from the initiation of study therapy through 14 days following treatment and not associated with virologic failure.*

4. first instance of alkaline phosphatase >3x ULN from the initiation of study therapy through 14 days following treatment and not associated with virologic failure.*

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

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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 7. The investigator's assessment of causality is required for each adverse event. Refer to Table 7 for instructions in evaluating adverse events.

Table 7 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; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse EventsAdverse Events and Patient/Device Events and Incidents

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 8 below.

Table 8 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Proportion of subjects achieving SVR_{12}	Wald Test	Full Analysis set	Missing=Failure
Secondary:			
Proportion of subjects achieving SVR_{24}	95% Confidence Interval (Asymptotic)	Full Analysis set	Missing=Failure

8.1.2 Safety Analyses

The All-Subjects-as-Treated population will be employed for safety analyses. For this protocol, the proportion of subjects who experience adverse events of elevated laboratory values that are reported as ECIs described in section 7.2.3.2 during the treatment period are pre-specified as events of clinical interest and will be estimated.

8.1.3 Power and Sample Size

This study will allocate 200 subjects into a single arm. Assuming a true response rate of at least 85%, the study has over 99% power to demonstrate that the SVR_{12} rate is superior to the historical reference rate of 70% at an overall one-sided 2.5% alpha-level. The rationale for the historical reference rate is in section 4.2.2.

8.2 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.2.1 Responsibility for Analyses

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. Certain specific analyses such as PK, pharmacogenetics and resistance will be the responsibility of the appropriate departments of the SPONSOR.

This is a single-arm study. Therefore, the subjects, study site personnel, and SPONSOR will not be blinded to the treatment arm.

8.2.2 Hypothesis/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed in the following sections.

8.2.3.1 Efficacy/Pharmacokinetic Endpoints

8.2.3.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.3.1.

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

The secondary efficacy endpoint is the proportion of subjects achieving SVR_{24}.

8.2.3.1.2 Pharmacokinetic Endpoints

Additional details are in Section 4.2.3.3.

The primary PK endpoints for MK-5172 and MK-8742 are C_{2hr} and C_{trough}. Additional PK parameters such as AUC_{0-24} may be calculated using population pharmacokinetic modeling approaches.

8.2.3.1.3 Exploratory Endpoints

1) The proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA<LLOQ at Week 2, 4 and 12 and the proportion of subjects achieving SVR_4.

2) Longitudinal HRQOL scores and change in HRQOL scores from baseline HRQOL scores

   a. SF-36v2® eight health domain scores (Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health), and the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores

   b. EQ-5D-5L Health State and VAS scores

   c. FACIT-Fatigue Scale score

   d. Total CLDQ-HCV score and CLDQ-HCV Domain (Activity/Energy, Emotion, Worry, System) scores

   e. Work Productivity and Activity Impairment scores

3) The emergence of viral resistance-associated variants (RAVs) to MK-5172 or MK-8742 when administered as part of a combination regimen.

4) The relationship between genetic variation and subject response to the treatment(s) administered.

5) The proportion of subjects who develop HIV-1 virologic failure (HIV-1 RNA ≥200 copies/mL, confirmed on 2 consecutive tests at least 2 weeks apart in subjects compliant with their HIV ARV therapies) during protocol therapy.

6) Changes in CD4+ T-cell counts from baseline.

8.2.3.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.2 and events of clinical interest (ECIs) are defined in Section 7.2.3.2. For this protocol, the proportion of subjects who experience adverse events of elevated laboratory values that are reported as ECIs described in section 7.2.3.2 during the study therapy period are pre-specified as events of clinical interest and will be estimated.

The following events will also be investigated: the proportion of subjects with adverse experiences of the following types at any time during the study therapy period: (1) at least one adverse experience; (2) a drug-related adverse experience; (3) a serious adverse experience; (4) a serious and drug-related adverse experience and (5) an adverse experience leading to discontinuation.

Serious adverse experiences will continue to be collected throughout the study.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all allocated subjects who receive at least one dose of study treatment.

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary efficacy endpoint (SVR_{12}) and secondary endpoints. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoints. Potential violations that may result in the exclusion of a subject from the Per-Protocol population include:

- The subject did not meet specific inclusion/exclusion criteria:
    - The subject is infected with HCV of genotype other than GT 1/4/6, at entry or during the course of the study, including a mixed GT infection (with a non-GT 1, 4, or 6) or non-typeable genotype
    - Subject is not co-infected with HIV-1 or HIV viral load not well controlled
- The subject received concomitant medications that are prohibited due to their potential to result in a clinically significant lowering of the MK-5172 or MK-8742 concentrations (see Section 5.5 for specific details of prohibited medications). Further, any co-administered medication, currently unidentified, but for which subsequent clinical DDI data indicate that co-administration with MK leads to a clinically significant lowering of MK concentrations.
- 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 as described above 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.

Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one 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 8.2.5.2 Statistical Methods.

8.2.5 Statistical Methods

The approach to handling missing data for efficacy analyses is described in Section 8.2.5.1. A summary of the analysis strategy for efficacy variables is shown in Table 9. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

Statistical inference for safety analyses are described in Section 8.2.5.2.

8.2.5.1 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 the 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 worse 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 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 violation, 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 (MAR) assumption is reasonable. The approaches to address this type of missing data depend on the analytical strategy, and they are described in the following sections.

In addition, a missing baseline/Day1 HCV RNA result will be replaced with a screening result, if available. Missing values in the health-related quality of life data will not be imputed.

Approaches to handle non-intermittent missing values due to prematurely discontinuing from study:

- Treatment-Related Discontinuation = Failure (TRD=F) approach: The treatment related type 2 missing will be considered as failure; whereas the subjects who have the type 3 missing value and 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.

- Missing=Failure (M=F) approach: Any non-intermittent missing (i.e., the type 2 and 3 missing) will be imputed as failure, regardless of the reason for study discontinuation.

Proportions of Subjects With Virologic Responses

For the primary efficacy analysis to estimate the proportion of subjects achieving SVR_{12}, a Wald test will be performed to ascertain whether the true SVR_{12} is at least 70%, the historical reference rate (see Section 4.2.2). In order to evaluate this criterion, a hypothesis of H_0: $p \leq 0.70$ will be tested against the alternative H_1: $p > 0.70$, where p is the proportion of subjects achieving SVR_{12}. A one-sided Wald test will be conducted at the $\alpha=0.025$ significance level. Rejection of the null hypothesis will lead to a conclusion that the true proportion of subjects achieving SVR_{12} is >70%.

Additional details with respect testing the primary hypothesis, including multiplicity considerations, are provided in Section 8.2.6.

The missing data approach of M=F described above will be utilized for the primary analysis.

Sensitivity analyses will be performed for the primary endpoint using the PP population and the TRD=F missing data approach.

Table 9 includes a summary of the key efficacy analyses.

Table 9 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time point)	Primary vs Secondary Approach†	Statistical Method	Analysis Population	Missing Data Approach‡
Primary:				
Proportion of subjects achieving SVR_{12}	P	Wald Test	FAS	M=F
Proportion of subjects achieving SVR_{12}	S	Wald Test	PP	TRD=F
Secondary:				
Proportion of subjects achieving SVR_{24}	P	95% Confidence Interval (Asymptotic)	FAS	M=F
Proportion of subjects achieving SVR_{24} [4]	S	95% Confidence Interval (Asymptotic)	PP	TRD=F

† P=Primary approach; S=Secondary approach.
‡ Imputation for specific missing values described in Section 8.2.5.1
OF = Observed Failure
M=F = Missing = Failure
PP = Per Protocol
FAS = Full Analysis Set

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

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 4.2.3.1.1.2.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences and laboratory parameters.

The proportion of subjects with adverse experiences of elevated laboratory values that are reported as ECIs described in section 7.2.3.2 during the study therapy period are pre-specified as events of clinical interest and will be provided along with the corresponding 95% confidence intervals.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and

serious, and who discontinued due to an AE will be summarized in the same manner (Table 10).

Missing values will be handled using the Data-As-Observed (DAO) approach, that is, any missing values will be excluded from the analysis.

Table 10 Analysis Strategy for Safety Parameters

Safety Endpoint†	95% CI	Descriptive Statistics
AEs of elevated laboratory values that are reported as ECIs	X	X
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Specific AEs or SOCs		X
Change from Baseline Results (laboratory)		X

†Adverse experiences refer to both clinical and laboratory AEs.
95% confidence intervals will be calculated using the Clopper-Pearson method.
Note: SOC = System Organ Class; X = results will be posted

8.2.5.3 Summaries of Baseline Characteristics, Demographics and other Analyses

Demographic and Baseline Characteristics

No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, enrolled, the primary reasons for screen failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, and genotype subtype), primary and secondary diagnoses, and prior and concomitant therapies will be summarized using descriptive statistics for continuous or categorical variables, as appropriate. Summary statistics for the baseline efficacy measure (HCV RNA) will also be provided.

Pharmacokinetic Analyses

Summary statistics for the concentrations of MK-5172 and MK-8742 will be provided.

Viral Resistance Measurements

Viral resistance testing will focus on the entire NS3/4A and NS5A regions for all subjects and for those who meet the subject virologic failure criteria (see Section 4.2.3.1.1.2).

Patient-Reported Outcomes Measurement

Each questionnaire will be scored for each subject at each measured time point according to the developers' scoring algorithms.

- The SF-36v2® includes eight health domain scores (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) ranging from 0 to 100, with 100 representing the best health status. The two summary scores for physical and mental health components, PCS and MCS, are calculated using the individual domain scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10.

- EQ-5D-5L subject's health state is summarized with a 5-digit number which represents the subject's response to each of the five dimensions. Each digit ranges from 1 (no problems) to 5 (extreme problems). The 5-digit number can range from 11111 to 55555, but has no arithmetic properties. The EQ-5D-5L health state can then be converted into a single index value. The index values are country-specific. EQ-5D-5L VAS scores range from 0 to 100, anchored on 100=the best health you can imagine and 0=the worst health you can imagine.

- FACIT-Fatigue Scale score will yield a summed total score of the 13-item responses ranging between 0 and 52, with 52 representing the best possible well-being (e.g. less fatigue).

- CLDQ-HCV scores will be calculated for each of the four domains (Activity/Energy, Emotion, Worry and Systemic) by summing the responses to the corresponding questions for each domain and dividing by the number of corresponding questions in each domain. The total CLDQ-HCV score will be calculated by summing the four domain scores and dividing by the total number of domains. The possible range of scores is from 1 to 7, with higher scores representing better HRQOL.

- Work Productivity and Activity Impairment Scores:

    - Work Impairment Domain: Assessed in those reporting being employed at the time of completing the questionnaire

        - Absenteeism scores: productivity loss due to health-related absence from work which includes personal time off, sick days off work, duration of short and/or long term work disability or worker's-compensated days

        - Presenteeism scores: represents reduction in performance or productivity while at work due to Hepatitis C, range from 0 (Hepatitis C had no effect on work) to 10 (Hepatitis C completely prevented me from working)

    - Activity Impairment Domain Scores: represents impairment in daily activities other than work due to hepatitis C, range from 0 (Hepatitis C had no effect on my daily activities) to 10 (Hepatitis C completely prevented me from doing my daily activities).

Descriptive summary statistics will be provided to assess PRO compliance (% compliance among subjects eligible to complete the PROs), longitudinal HRQOL scores and change in HRQOL scores from baseline HRQOL scores at post-baseline time points. In addition, descriptive summary statistics will be provided for change in HRQOL scores from baseline HRQOL scores at follow-up weeks 12 and 24 stratified by SVR12 and SVR24 status. Missing data will not be imputed, and the analyses will be based on observed data only. These analyses will be based on the FAS population. No multiplicity adjustment will be applied.

Proportion of Subjects Who Develop HIV-1 Virologic Failure

The proportion of subjects who develop HIV-1 virologic failure (HIV-1 RNA ≥200 copies/mL using the COBAS® AmpliPrep/COBAS® Taqman® HIV Test, version 2.0 ® assay confirmed on 2 consecutive tests at least 2 weeks apart, in subjects compliant with their HIV ARV therapies) during protocol therapy will be estimated at Week 4, Week 8 and Week 12 and the end of treatment visit. For some subjects, Week 12 and the end of treatment visit may be the same. The corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method. Missing data will not be imputed and the analysis will be based on observed data only (DAO approach).

CD4+ T-Cell Count Changes

Change from baseline in CD4+ T-cell counts will be estimated along with corresponding confidence intervals at Week 4, Week 8 and Week 12, and at the end of treatment visit. For some subjects, Week 12 and the end of treatment visit may be the same. Missing data will not be imputed and the analysis will be based on observed data only (DAO approach).

8.2.6 Multiplicity

As there is only a single primary efficacy hypothesis which is being conducted at the one-sided α=0.025 level, no multiplicity adjustment is needed for the primary efficacy analysis. The secondary efficacy objectives are estimation objectives, are supportive in nature and have no associated hypotheses. Therefore, no multiplicity adjustment is necessary for the secondary efficacy analysis.

There will be no multiplicity adjustments applied to the safety summaries.

8.2.7 Sample Size and Power calculations

8.2.7.1 Efficacy Analysis

Two hundred (200) subjects will be allocated in this study. As the primary analysis will be conducted on the FAS population, it is assumed that all 200 allocated subjects will be included in the primary analysis. Assuming a true SVR_{12} of 85%, this study has >99.9% power to demonstrate that the true rate is >70%. If the true SVR_{12} is 80%, the study has 93.1% power to demonstrate that the true rate is >70%, while the power drops to 40.8% if the true SVR_{12} is only 75%.

The minimum number of subjects needed to achieve SVR_{12} and satisfy the criterion for the primary efficacy hypothesis is 152 out of 200 subjects (76.0%). If the observed SVR_{12} proportion is 76.0% (152/200), the corresponding 95% CI for SVR_{12} would be (70.1%, 81.9%) and the primary efficacy hypothesis will be met.

8.2.7.2 Safety Analysis

The primary safety objective of this study will be assessed by a review of the accumulated safety data. Certain safety endpoints of special interest have been identified in Section 8.2.5.

The probability of observing at least one specific adverse event in this study depends on the number of subjects treated and the underlying percentage of subjects with that adverse event in the study population. For example, if the underlying incidence of a specific adverse event is 0.8% (1 of every 124 subjects receiving MK-5172 and MK-8742), there is an 80% chance of observing at least one incident of that specific adverse event among 200 subjects in this study. If a given specific adverse event is not observed among the 200 subjects in the study, the probability is 97.5% that the underlying percentage of subjects with that adverse event is <1.83% (one in every 54 subjects in the study).

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of subjects with a specific adverse event given various hypothetical observed number of subjects with that specific adverse event within the study are provided in Table 11.

These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934).

Table 11 Estimate of Incidence of a Specific Adverse Event and 95% Upper Confidence Bound Based on a Hypothetical Number of Subjects with that Specific Adverse Event Among 200 Subjects

Hypothetical Number of Subjects With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[†]
1	0.5%	2.8
2	1.0%	3.6
5	2.5%	5.7
10	5.0%	9.0
20	10.0%	15.0
30	15.0%	20.7
50	25.0%	31.6
[†] Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).		

8.2.8 Subgroup Analyses and Effects of Baseline Factors

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

- Sex (female, male)
- GT (1a, 1 non-a, 4, 6)
- *IL28B* CC genotype vs non-CC genotype
- HCV RNA at baseline, low (≤800,000 IU/mL) versus high (>800,000 IU/mL)
- Stage of fibrosis (Non-cirrhotic vs Cirrhotic)
- IFN Treatment Eligibility Status

8.2.9 Interim Analyses

No formal interim analyses are planned for this study; however, routine in-house medical monitoring will be conducted for this open-label study.

8.2.10 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 MK-5172A 100mg/50mg. The "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study medication for that subject. Note, the date of the last dose of study medication would be the last scheduled day for treatment administration for subject who completed the assigned treatment.

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.

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 12.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form
MK-5172A 100mg/50mg (100 mg MK-5172/50 mg MK-8742)	Tablet

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 bi-monthly finished good bottles. No kitting is required.

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 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 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 member 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 or through a secure password-protected electronic portal 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 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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.

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