

THE LANCET

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: Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2014; published online Nov 11. [http://dx.doi.org/10.1016/S0140-6736\(14\)61793-1](http://dx.doi.org/10.1016/S0140-6736(14)61793-1).

Supplementary Appendix

All investigators who enrolled mono- and co-infected patients

Australia: J. Davis, W. Sievert, S. Strasser, A. Thompson, and E. Tse;

Canada: S. Feinman, W. Ghesquiere, S. Lee, M.E. Morin, A. Ramji, and E. Tam;

Denmark: P. Christensen, J. Gerstoft, J. Hansen, A. Laursen, and N. Weis;

France: L. Alric, M. Bourliere, J. P. Bronowicki, D. Guyader, C. Hezode, D. Larrey, P. Marcellin, S. Metivier, S. Pol, V. Ratziu, L. Serfaty, and F. Zoulim;

Hungary: G. Horvath, B. Hunyady, M. Makara, and K. Werling;

Israel: Y. Baruch, Z. Ben Ari, Y. Lurie, O. Shibolet, and E. Zuckerman;

New Zealand: E. Gane;

Puerto Rico: G. Sepulveda;

Spain: J. Mallolas, M. Laguno, M. Martínez-Rebollar;

Sweden: L. Flamholc, M. Lagging, F. Sund, and O. Weiland;

Turkey: A. Celebi, and O. Yuksel;

United States: V. Ankoma-Sey, L. Balart, D. Bernstein, E. DeJesus, J. Galati, G. Galler, R. Ghalib, M.

Kugelmas, E. Lawitz, V. Luketic, A. Murillo, R. Nahass, A. Odio, B. Pearlman, C. Peine, D. Pound, N.

Ravendhran, F. Regenstein, L. Rossaro, M. Russo, K. Sherman, M. Sulkowski, H. Tatum, J. Vierling, and P. Winkle.

Supplementary Table S1: Proportion of patients with HCV RNA <25 IU/mL at various times during and after treatment with grazoprevir + elbasvir with or without ribavirin

Arm	HCV RNA <25 IU/mL, n/m (%)					
	TW2	TW4	End of Therapy (EOT)	4 weeks after EOT (SVR4)	8 weeks after EOT (SVR8)	12 weeks after EOT (SVR12)
HCV Mono-infected, 8 weeks + RBV	25/30 (83)	30/30 (100)	30/30 (100)	28/30 (93)	24/30 (80)	24/30 (80)
HCV Mono-infected, 12 weeks + RBV	70/85 (82)	81/85 (95)	82/85 (96)	80/85 (94)	79/85 (93)	79/85 (93)
HCV Mono-infected, 12 weeks No RBV	36/44 (82)	44/44 (100)	44/44 (100)	43/44 (98)	43/44 (98)	43/44 (98)
HIV/HCV Co-infected, 12 weeks + RBV	26/29 (90)	29/29 (100)	29/29 (100)	28/29 (97)	28/29 (97)	28/29 (97)
HIV/HCV Co-infected, 12 weeks No RBV	23/30 (77)	30/30 (100)	28/30 (93)	27/30 (90)	26/30 (87)	26/30 (87)

n/m=the number of patients with HCV RNA <25 IU/mL divided by the number of patients in the treatment arm. ;

TW=treatment week; RBV=ribavirin

There is 100% concordance between SVR8 and SVR12.

Supplementary Table S2: Safety of grazoprevir + elbasvir

	HCV Mono-infected			HIV/HCV Co-infected		Total
Ribavirin	+ RBV	+ RBV	No RBV	+ RBV	No RBV	± RBV
Duration of treatment (weeks)	8	12	12	12	12	8 or 12
No. of patients	30	86	43	29	30	218
Common AEs ≥10% in any group, n (%)						
≥1 AE	26 (87)	65 (76)	38 (88)	19 (66)	15 (50)	163 (75)
Fatigue	14 (47)	23 (27)	10 (23)	2 (7)	2 (7)	51 (23)
Headache	7 (23)	17 (20)	15 (35)	4 (14)	1 (3)	44 (20)
Nausea	8 (27)	16 (19)	7 (16)	0 (0)	1 (3)	32 (15)
Insomnia	3 (10)	12 (14)	3 (7)	2 (7)	0 (0)	20 (9)
Diarrhea	5 (17)	10 (12)	5 (12)	1 (3)	0 (0)	21 (10)
Pruritus	6 (20)	6 (7)	0 (0)	3 (0)	0 (0)	15 (7)
Dizziness	3 (10)	7 (8)	4 (9)	0 (0)	0 (0)	14 (6)
Abdominal pain, upper	2 (7)	9 (10)	1 (2)	0 (0)	0 (0)	12 (6)
Asthenia	1 (3)	3 (3)	3 (7)	4 (14)	1 (3)	12 (6)
Accidental overdose	4 (13)	6 (7)	1 (2)	1 (3)	0 (0)	12 (6)
Dyspnea	4 (13)	5 (6)	1 (2)	1 (3)	0 (0)	11 (5)
Rash	0 (0)	9 (10)	2 (5)	0 (0)	0 (0)	11 (5)
Decreased appetite	4 (13)	2 (2)	2 (5)	0 (0)	1 (3)	9 (4)
Sleep disorder	1 (3)	2 (2)	2 (5)	4 (14)	0 (0)	9 (4)
Disturbance to attention	3 (10)	1 (1)	0 (0)	0 (0)	0 (0)	4 (2)
Mood swings	3 (10)	0 (0)	1 (2)	0 (0)	0 (0)	4 (2)
Lowest laboratory values						
Alanine aminotransferase (IU/L), n (%)						
Grade 1: 1.25-2.5 x ULN	0 (0)	6 (7)	2 (5)	0 (0)	2 (7)	10 (5)
Grade 2: 2.6-5.0 x ULN	1 (3)	4 (5)	0 (0)	0 (0)	0 (0)	5 (2)
Grade 3: 5.1-10.0 x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4: >10.0 x ULN	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)
Aspartate aminotransferase (IU/L), n (%)						
Grade 1: 1.25-2.5 x ULN	0 (0)	6 (7)	1 (3)	0 (0)	2 (7)	9 (4)
Grade 2: 2.6-5.0 x ULN	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)
Grade 3: 5.1-10.0 x ULN	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)
Grade 4: >10.0 x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elevation of total bilirubin (mg/dL), n (%)						
Grade 1: 1.1-1.5 x ULN	3 (10)	20 (24)	1 (2)	4 (14)	2 (7)	30 (14)
Grade 2: 1.6-2.5 x ULN	4 (13)	10 (12)	0 (0)	5 (17)	1 (3)	20 (9)
Grade 3: 2.6-5.0 x ULN	2 (7)	2 (2)	0 (0)	0 (0)	0 (0)	4 (2)
Grade 4: >5.0 x ULN	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Albumin (g/dL), n (%)						
Grade 1: 3.0 - <LLN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 2: 2.0 - 2.9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3: <2.0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lymphocytes (x 1000/μL)						
Grade 1: 0.60 - 0.65	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	2 (1)
Grade 2: 0.50 - 0.599	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)	2 (1)
Grade 3: 0.35 - 0.499	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4: <0.35	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Platelets (x 1000/ μ L), n (%)						
Grade 1: 100-<140	0 (0)	0 (0)	2 (5)	0 (0)	1 (3)	3 (1)
Grade 2: 50-<100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3: 25-<50	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4: <25	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophils (x 1000/ μ L), n (%)						
Grade 1: 1.00-1.96	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	3 (1)
Grade 2: 0.75-0.999	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3: 0.50-0.749	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4: <0.50	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

All adverse events, serious adverse events and lowest laboratory values were recorded from the time the consent form was signed through 14 days after cessation of treatment. The incidence of common adverse events ($\geq 10\%$ in any group; listed in decreasing frequency based on the group of all patients) and laboratory changes are shown. The relatedness (probable or possible) of the adverse event to the regimen was determined by the investigator. Patients could have had more than 1 adverse event.

Supplementary Table S3: Proportions of patients with or without resistance-associated variants (RAVs)* who did or did not achieve SVR12 (ITT[†])

	Number (%) of patients who achieved SVR12	Number (%) of patients who did not achieve SVR12	Total number (%) of patients
NS3			
No RAVs	130 (60)	11 (5)	141 (65)
≥1 RAV	68 (31)	7 (3)	75 (35)
Total	198 (92)	18 (8)	216 (100)
p-value for the Chi-Squared Test: 0.698			
NS5A			
No RAVs	181 (84)	10 (5)	191 (88)
≥1 RAV	17 (8)	8 (4)	25 (12)
Total	198 (92)	18 (8)	216 (100)
p-value for the Chi-Squared Test: <0.001			

*The table reports the following RAV(s) for NS3: 36A/G/L/M/I, 54A/C/G/S, 55A/I, 56H, 80K/R, 107I, 122A/G/R, 132V, 155X, 156S/T/V/F/G, 158I, 168X, 170A/F/T/V and 175L, and the following RAV(s) for NS5A: 28T/V, 30E/H/R/K/Y, 31M/V, 58D and 93H/C/N.

[†] This ITT analysis included all patients who received at least one dose of study drug, and included 6 patients who were lost to follow-up or discontinued early for reasons other than virologic failure.

Supplementary Table S4: Resistance-associated variants at baseline and at virologic failure

Patients	Breakthrough or relapse	Duration of Regimen (weeks)	GT	RBV	Baseline fibrosis score	Failure Time Point	RAVS at baseline		RAVS at failure	
							NS3	NS5A	NS3	NS5A
HIV/HCV Co-infected	Breakthrough	12	1a	NO	F0-F2	TW8 [†]	WT	M28V	V36M A156T*	M28G [‡]
			1a	NO	F0-F2	TW8 [†]	WT	WT	V36M/V A156T*	M28T* Q30H* H58D/H [‡]
	Relapse	12	1a	YES	F0-F2	FU4	WT	Y93N*	WT	Y93N*
HCV Mono-infected	Breakthrough	12	1b	YES	F0-F2	TW8	S122T‡ V132I‡	WT	New infection with GT2b [¶]	
	Relapse	12	1a	YES	F0-F2	FU4	Q80K	Y93N*	(Q80K) Y56H* D168A*	(Y93N*)
			1b	YES	F0-F2	FU12	S122N/S	WT	S122N/S	L31M*, Y93H*
			1a	NO	F0-F2	FU4	WT	Q30H* Y93H*	D168A*	(Q30H* Y93H*)
		8	1a	YES	F0-F2	FU12	WT	WT	WT	WT
			1a	YES	F0-F2	FU12	Q80K	WT	(80K) T95S	WT
			1a	YES	F0-F2	FU4	Q80K	WT	(Q80K) D168A*	Y93N*
			1a	YES	F0-F2	FU4	R62K H110Q I170V	WT	(I170V) A156T*	L31M* V37M Y93H*
			1a	YES	F0-F2	FU12	Q80K	L31M*	(Q80K) Y56H* D168N*	Q30R* (L31M*)

* Variants with ≥ 5 -fold reduced susceptibility to grazoprevir or elbasvir

[†] 2 HIV/HCV co-infected patients with breakthrough had plasma levels of grazoprevir and/or elbasvir less than the lower bound of the 95% confidence interval

‡ EC50 in replicon assay not determined.

^{||} This patient did not receive grazoprevir for the first month of treatment and only received only elbasvir + ribavirin for the first month of treatment.

[¶] Mixed infection with GT1b and GT2b at baseline cannot be excluded.

() = variants that pre-existed prior to treatment and persisted through virologic failure.

No patient had a history of reported noncompliance, HIV breakthrough, concomitant medication of concern, or serious adverse event.

Virologic breakthrough was defined as a confirmed HCV RNA ≥ 25 IU/mL after being < 25 IU/mL previously. Relapse was defined as a confirmed HCV RNA ≥ 25 IU/mL following end of all study therapy after becoming undetectable (HCV RNA < 9.3 IU/mL) at end of treatment. For both virologic breakthrough and relapse, confirmation was defined as a result of HCV RNA ≥ 25 IU/mL from a separate blood draw repeated within 2 weeks. The Failure Time Point was the time that HCV RNA was ≥ 25 IU/mL after being < 25 IU/mL or undetectable previously.

In vitro, A156T and D168A/N conferred 2-280-fold reduced susceptibility to grazoprevir, and M28T, L31M, Q30R/H and Y93H/N conferred 20- to 2000-fold reduced susceptibility to elbasvir.

Supplementary Table S5: Proportions of patients with resistance-associated variants at baseline who did or did not achieve SVR12

HCV Protein	NS3															NS5A				
Amino Acid Position*	36	54	55	56	80	107	122	132	155	158	156	168	170	175	28	30	31	58	93	
Number of patients with RAV, n (%)	2 (1)	5 (2)	7 (3)	0 (0)	43 (20)	1 (<1)	15 (7)	0 (0)	2 (1)	0 (0)	0 (0)	1 (<1)	9 (4)	1 (<1)	12 (6)	3 (1)	5 (2)	0 (0)	9 (4)	
Number of patients with RAV who did not achieve SVR12, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	6 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (1)	1 (<1)	1 (<1)	0 (0)	5 (2)	
Number of patients with RAV who did achieve SVR12, n (%)	2 (1)	5 (2)	7 (3)	0 (0)	37 (17)	1 (<1)	15 (7)	0 (0)	2 (1)	0 (0)	0 (0)	1 (<1)	8 (4)	1 (<1)	10 (5)	2 (1)	4 (2)	0 (0)	4 (2)	

The total number of patients in this trial was 218. The total numbers of NS3 and NS5A sequences were 216.

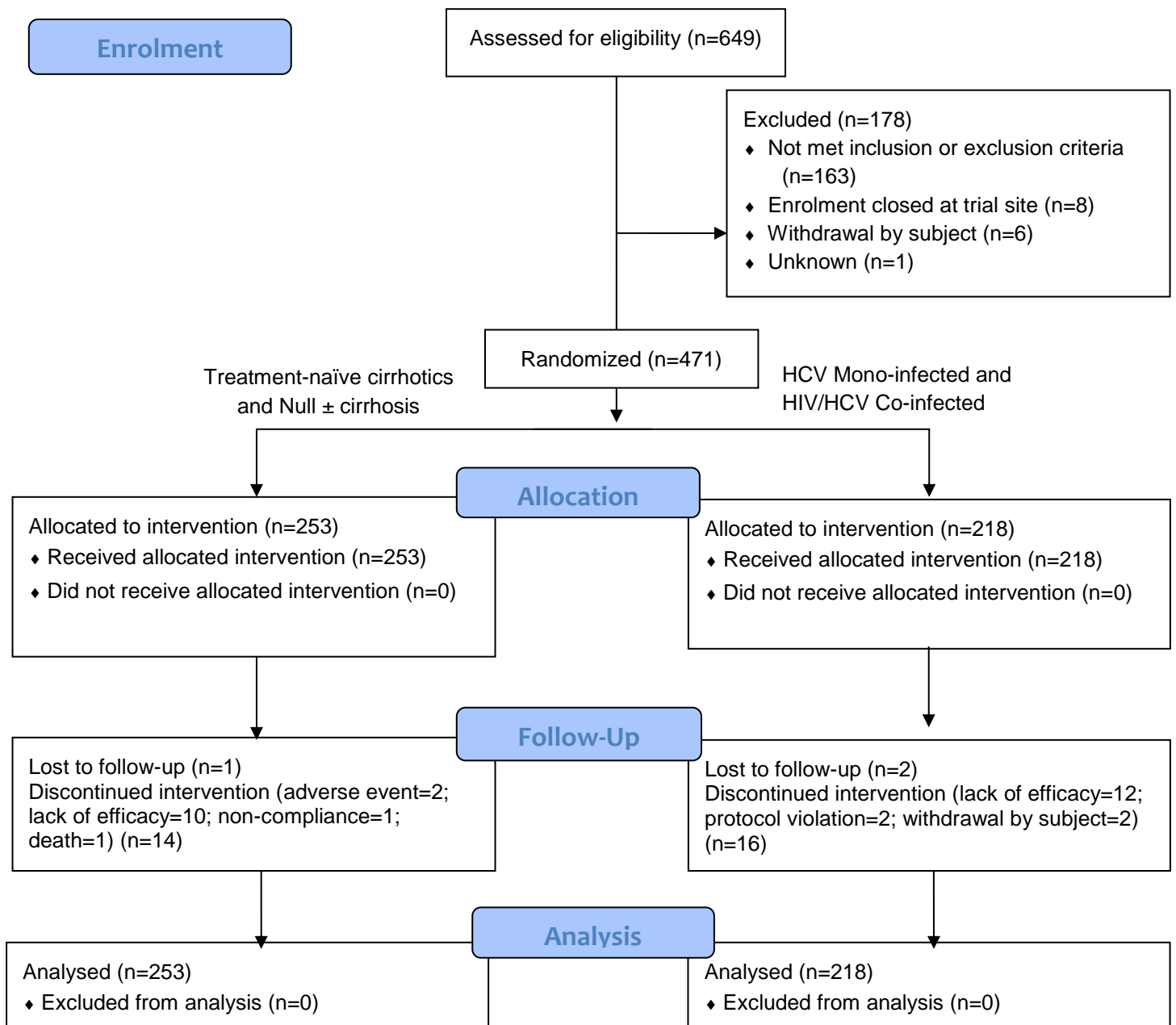
Shading indicates amino acid positions Y56H and D168X which are associated with resistance to grazoprevir, and 30E/H/R/K/Y, 31M and 93H/C/N which are associated with resistance to elbasvir. *In vitro*, A156T and D168A/N conferred 2-280-fold reduced susceptibility to grazoprevir, and M28T, L31M, Q30R/H and Y93H/N conferred 20- to 2000-fold resistance to elbasvir.

*The table reports the following RAV(s) for NS3: 36A/G/L/M/I, 54A/C/G/S, 55A/I, 56H, 80K/R, 107I, 122A/G/R, 132V, 155X, 156S/T/V/F/G, 158I, 168X, 170A/F/T/V and 175L, and the following RAV(s) for NS5A: 28T/V, 30E/H/R/K/Y, 31M/V, 58D and 93H/C/N. Patients could have had more than one RAV.

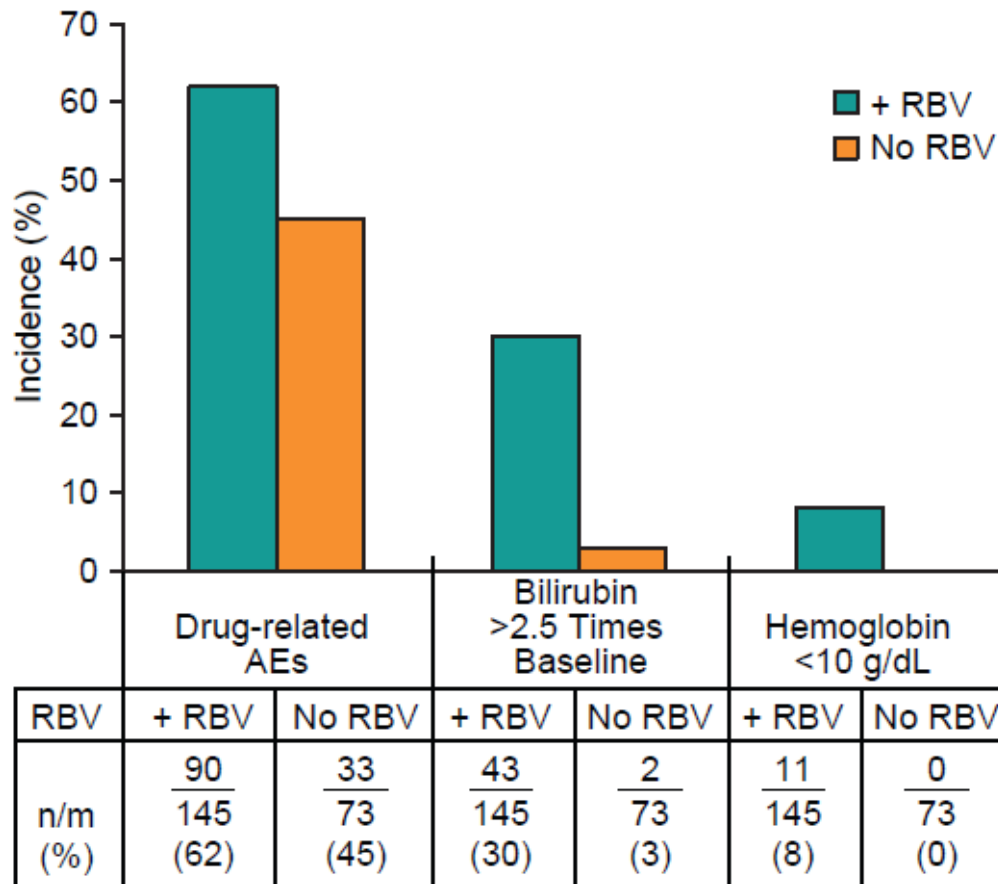
Supplementary Table S6: Geographical distribution of patients

	HCV Mono-infected				HIV/HCV Co-infected			All patients
Ribavirin	+ RBV	+ RBV	No RBV	± RBV	+ RBV	No RBV	± RBV	± RBV
Duration of treatment (weeks)	8	12	12	8 or 12	12	12	12	8 or 12
No. of patients	30	85	44	159	29	30	59	218
Geographical distribution of patients, n (%)								
United States, Canada & Puerto Rico	16 (53)	48 (56)	27 (61)	91 (57)	4 (14)	6 (20)	10 (17)	101 (46)
Denmark & France	4(13)	21 (25)	9 (20)	34 (21)	14 (48)	12 (40)	26 (44)	60 (28)
Israel, Spain, Hungary, Sweden & Turkey	3 (10)	14 (16)	4 (9)	21 (13)	11 (38)	8 (27)	19 (32)	40 (18)
Australia & New Zealand	7 (23)	2 (2)	4 (9)	13 (8)	0 (0)	4 (13)	4 (7)	17 (8)

Supplementary Figure S1: CONSORT Flow Diagram



Supplementary Figure S2: Incidence of selected adverse events and laboratory values in combined co-infected and mono-infected patients



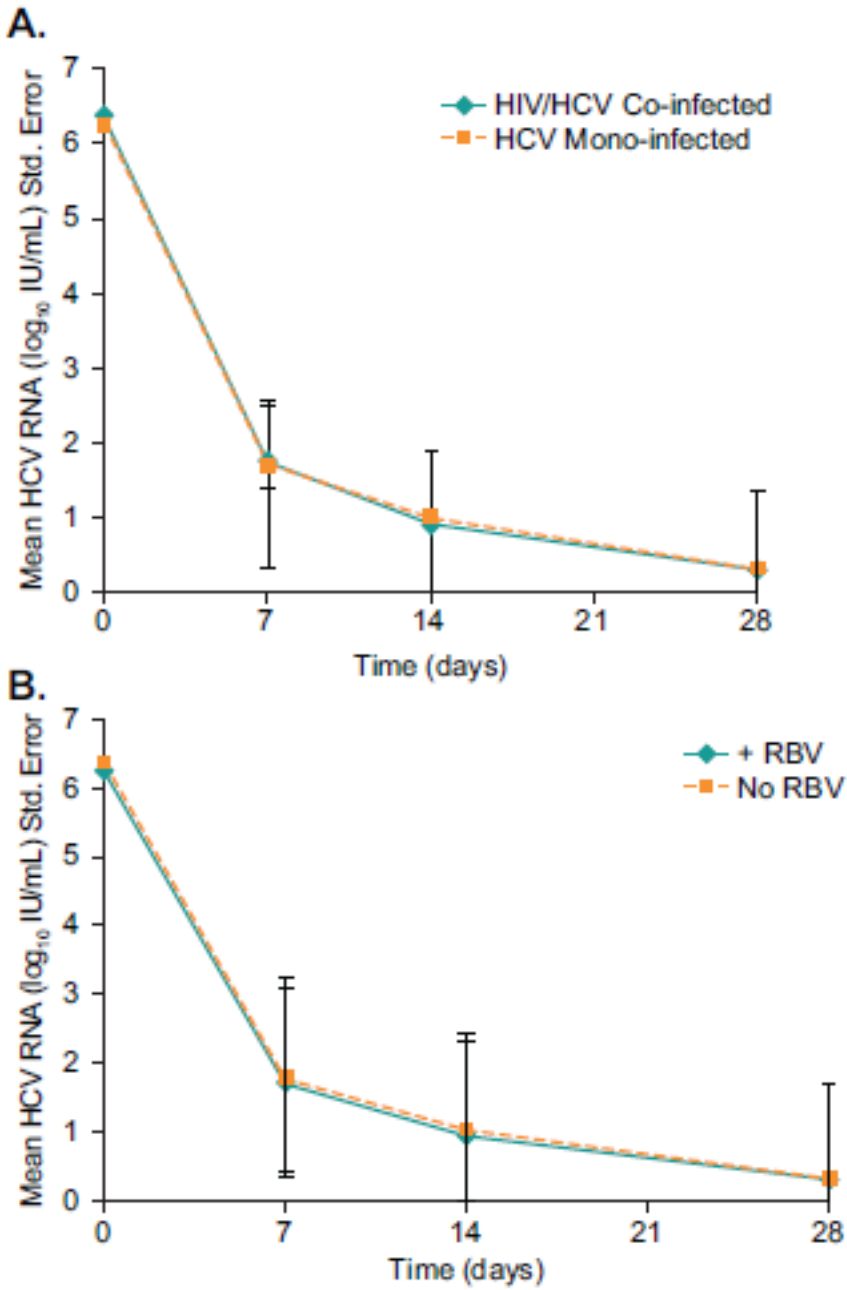
The incidences (n/m, number/subtotal) of drug-related adverse events, bilirubin values greater than 2.5 times the baseline, and hemoglobin values less than 10 grams per deciliter are shown for arms that received grazoprevir + elbasvir + RBV (+ RBV) or grazoprevir + elbasvir (No RBV).

* Baseline platelet count missing for one patient

RBV, ribavirin; SD, standard deviation; Non-White, Black or African-American or Asian or Multiple; GT, genotype; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Baseline results (HIV RNA, HCV RNA, hemoglobin, albumin, ALT, AST, bilirubin, platelets) were determined on samples taken on day 1. HCV genotyping was conducted using the Versant HCV genotype (LiPA) 2.0 manufactured by Innogenetics (Ghent, Belgium). Plasma samples were collected at screening for *IL28B* genotype evaluation (rs12979860: CC vs non-CC).

Supplementary Figure S3: HCV RNA decreases in mono- and co-infected patients during the first 28 days of treatment



RBV = ribavirin.

Mean HCV RNA (\log_{10} [IU/mL]) values and standard errors of the mean were calculated for days 0, 7, 14, 21 and 28. Panel A: HIV/HCV Co-infected vs. HCV Mono-infected; Panel B: grazoprevir + elbasvir + RBV vs. grazoprevir + elbasvir (No RBV).

Allocation Ratios

For Part A: Randomization will occur centrally using an interactive voice response system (IVRS). There are 3 treatment arms. Subjects will be assigned randomized treatment in a 2:2:3 ratio to one of the following treatment arms for GT 1b subjects, and in a 1:1 ratio to the first two treatment arms for GT1a subjects:

- grazoprevir 100 mg + elbasvir 20 mg + RBV
- grazoprevir 100 mg + elbasvir 50 mg + RBV
- grazoprevir 100 mg + elbasvir 50 mg

For Part B: Randomization will occur centrally using an interactive voice response system (IVRS). In Part B, there are 13 treatment arms. Subjects will be assigned and randomized based on subject population and disease characteristics (cirrhotic or non-cirrhotic).

Treatment Naïve (Non-cirrhotic: Arms 1-3):

GT1a subjects will be randomized to 3 treatment arms in a ratio of 2:1:2 to receive 8 weeks of open label grazoprevir 100 mg + elbasvir 50 mg + RBV, or 12 weeks of open label grazoprevir 100 mg + elbasvir 50 mg, +/- RBV. GT1 non-a subjects will all be allocated to receive 12 weeks of open label grazoprevir 100 mg + elbasvir 50 mg + RBV.

Treatment Naïve (Cirrhotic: Arms 4-7)

Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label grazoprevir 100 mg + elbasvir 50 mg, +/- RBV.

Null-responders (Cirrhotic or Non-cirrhotic: Arms 8-11):

Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label grazoprevir 100 mg + elbasvir 50 mg, +/- RBV.

Treatment Naïve with HIV co-infection (Non-cirrhotic: Arms 12-13):

Subjects will be randomized to 2 treatment arms in a ratio of 1:1 to receive 12 weeks of open label grazoprevir 100 mg + elbasvir 50 mg, +/- RBV.

Primary & Secondary Objectives

The following applies to Part A and Part B (unless otherwise specified):

As this is a hypothesis-generating study, there are no formal hypotheses for this study.

In subjects with chronic HCV GT1 infection with pre-treatment HCV RNA of at least 10,000

IU/mL:

Primary Objectives

(1) Objective: To evaluate the efficacy of each treatment arm of grazoprevir in combination with elbasvir +/- RBV 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 <25 IU/mL (either TD(u) or TND) 12 weeks after the end of all study therapy.

(2) Objective: To evaluate the safety and tolerability of grazoprevir in combination with elbasvir +/- RBV.

Note: For Part B, each treatment arm will be assessed for efficacy, safety, and tolerability (as defined above) within each subject population.

Secondary Objectives

The following applies to Part A and Part B (unless otherwise specified):

In subjects with chronic HCV GT1 infection with pre-treatment HCV RNA of at least 10,000

IU/mL:

(1) Objective: To evaluate the efficacy of each treatment arm of grazoprevir in combination with elbasvir +/- RBV as assessed by the time to first achievement of undetectable (TND) HCV RNA.

(2) Objective: To evaluate the efficacy of each treatment arm of grazoprevir in combination with elbasvir +/- RBV as assessed by the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA <25 IU/mL at Week 2, 4, and end of treatment visit for the 8 and 12 Week duration arms and, Week 2, 4, 12, and end of treatment visit for the 18 Week duration arm.

(3) Objective: To evaluate the efficacy of each treatment arm of grazoprevir in combination with elbasvir +/- RBV as assessed by the proportion of subjects achieving:
SVR4 (Sustained Virologic Response 4 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 4 weeks after the end of all study therapy.

SVR24 (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 24 weeks after the end of all study therapy.

(4) Objective: To evaluate the emergence of viral resistance-associated variants (RAVs) resistant to grazoprevir and elbasvir when administered as part of a combination regimen +/- RBV.

In Part B, the secondary objectives above will be evaluated within each subject population separately. In addition, the following objectives will also be evaluated for the HIV co-infected population:

(5) Objective: To evaluate the proportion of subjects who develop HIV-1 virologic failure (HIV-1 RNA \geq 200 copies/mL, confirmed on two consecutive tests at least 2 weeks apart, in subjects compliant with their HIV ARV therapies) during protocol therapy (only applicable for co-infected sub-population in part B of the study)

(6) Objective: To evaluate the effect of the study regimen on CD4+ T-cell counts (only applicable for co-infected sub-population in part B of the study)

Additional Exclusion Criteria

Additional exclusion criteria included alanine aminotransferase (ALT) >350 IU/mL, aspartate aminotransferase (AST) >350 IU/mL, creatinine clearance <50 mL/min, neutrophils <1.5 x 10³/μL (<1.2 x 10³/μL for Blacks), direct bilirubin >1.5 x upper limit of normal (ULN), platelets <150 x 10³/μL (Part A) or <125 x 10³/μL (Part B), and serum albumin <3.5 g/dL.

Masking/Blinding

In the RBV-containing arms, a double-blind/masking technique with elbasvir and placebo to elbasvir was used to maintain the blind/masking of treatment. The patient, investigator and study site personnel were blinded to the treatment group assignments but the sponsor was not. The RBV-free arm was not blinded to the dose of elbasvir. In Part B of this study, treatment-naïve, non-cirrhotic GT1a patients were randomized to 3 treatment arms in a ratio of 2:1:2 to receive 8 weeks of open label grazoprevir + elbasvir (50 mg once daily) + RBV, or 12 weeks of open label grazoprevir + elbasvir (50 mg once daily) ± RBV. GT1b (non-a) patients were all allocated to receive 12 weeks of open label grazoprevir + elbasvir (50 mg once daily) + RBV. Treatment-naïve, non-cirrhotic patients with HIV co-infection were randomized to 2 treatment arms in a ratio of 1:1 to receive 12 weeks of open label grazoprevir + elbasvir (50 mg once daily) ± RBV.

Power and Sample Size

Part A of this estimation study will randomize approximately 24 subjects in each of the treatment arms that include RBV, and 12 subjects in the treatment arm without RBV. Assuming a protocol violation rate of 10%, the per protocol (PP) population will include approximately 22 subjects per arm with RBV and 11 subjects in the arm without RBV. For the arms with RBV, if the SVR12 rate is approximately 82% (18 successes out of 22), the exact 95% CI is (60.8%, 94.4%). If the SVR12 rate is approximately 91% (20 successes out of 22), the exact 95% CI is (72.0%, 98.7%). For the arm without RBV, if the SVR12 rate is approximately 90% (10 successes out of 11), the exact 95% CI is (58.7%, 99.8%).

In part B, four subject populations (TN no cirrhosis, TN with cirrhosis, Null-responders no cirrhosis and with cirrhosis, and TN with HIV co-infection no cirrhosis) will be randomized according to the design as illustrated in the CONSORT Flow Diagram. Approximately 30 subjects from each subject population will be randomized to each treatment arm relevant to that subject population.



This document is the property of Merck and Merck owns the copyright.

Merck's policy on posting of study protocols on journal websites is described at the following link:

<http://www.merck.com/research/discovery-and-development/clinical-development/Merck-Guidelines-for-Publication-of-Clinical-Trials-and-Related-Works.pdf>

For publicly posted protocols, Merck redacts the background and rationale sections because these sections may contain proprietary information. Merck also redacts the names of any individuals due to privacy issues. The appendices are generally not provided because they may be lengthy and contain non-essential information. The publicly posted protocol includes all the key sections that are relevant to evaluating the study, specifically those sections describing the study objectives and hypotheses, the patient inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, the statistical analysis plan, and amendments relating to those sections.

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder.

TITLE:

A Phase II Randomized Clinical Trial to Study the Efficacy and Safety of the combination regimen of MK-5172 and MK-8742 +/-Ribavirin (RBV) in Subjects with Chronic Hepatitis C Virus Infection

IND NUMBER: 110,261

EudraCT NUMBER: 2012-003354-89

TABLE OF CONTENTS

SUMMARY OF CHANGES.....	10
PRIMARY REASON(S) FOR THIS AMENDMENT:	10
ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:.....	10
1.0 TRIAL SUMMARY.....	12
2.0 TRIAL DESIGN.....	14
2.1 Trial Design	14
2.2 Trial Diagram.....	18
3.0 OBJECTIVE(S) & HYPOTHESIS(ES).....	20
3.1 Primary Objective(s) & Hypothesis(es)	20
3.2 Secondary Objective(s) & Hypothesis(es).....	20
3.3 Exploratory Objectives.....	21
4.0 BACKGROUND & RATIONALE.....	22
4.1 Background	22
4.1.1 Pharmaceutical and Therapeutic Background	22
4.2 Rationale.....	23
4.2.1 Rationale for the Trial and Selected Subject Population	23
4.2.2 Rationale for MK-5172 and MK-8742 Dose Selection/Regimen/Modification	30
4.2.3 Rationale for Endpoints	37
4.2.3.1 Efficacy Endpoints.....	37
4.2.3.1.1 Measurements of HCV RNA (Part A and Part B)	37
4.2.3.1.1.1 Definition of Efficacy Endpoints (Part A and Part B)	38
4.2.3.1.1.2 Definition of Virologic Failure: Futility, Virologic Breakthrough, Rebound and Relapse	38
4.2.3.1.2 Viral Resistance Measurements (Part A and Part B).....	40
4.2.3.1.3 <i>IL28B</i> , ADME genes and HLA Measurements (Part A and Part B)	40
4.2.3.2 Patient Reported Outcome Endpoint (Part B only).....	41
4.2.3.3 Safety Endpoints (Part A and Part B)	41
4.2.3.4 Pharmacokinetic Endpoints (Part A and Part B).....	41
4.2.3.5 Planned Exploratory Biomarker Research (Part A and Part B).....	41

4.2.3.6	Future Biomedical Research (Part A and Part B)	42
5.0	METHODOLOGY	42
5.1	Entry Criteria.....	42
5.1.1	Diagnosis/Condition for Entry into the Trial	42
5.1.2	Subject Inclusion Criteria.....	43
5.1.3	Subject Exclusion Criteria	47
5.2	Trial Treatments.....	56
5.2.1	Dose Selection/Modification (Part A and Part B).....	58
5.2.1.1	Dose Selection	58
5.2.2	Timing of Dose Administration	60
5.2.3	Trial Blinding/Masking.....	61
5.3	Randomization or Treatment Allocation.....	61
5.4	Stratification.....	62
5.5	Concomitant Medications (allowed & prohibited)	62
5.6	Rescue Medications & Supportive Care	64
5.7	Diet/Activity/Other Considerations.....	65
5.8	Subject Withdrawal/Discontinuation Criteria (Part A and Part B)	66
5.9	Subject Replacement Strategy (Part A and Part B)	67
5.10	Beginning and End of the Trial	67
5.11	Clinical Criteria for Early Trial Termination	68
6.0	TRIAL FLOW CHART	70
7.0	TRIAL PROCEDURES	79
7.1	Trial Procedures	79
7.1.1	Administrative Procedures.....	79
7.1.1.1	Informed Consent.....	79
7.1.1.1.1	General Informed Consent.....	79
7.1.1.1.2	Consent and Collection of Specimens for Future Biomedical Research.....	80
7.1.1.2	Inclusion/Exclusion Criteria	80
7.1.1.3	Subject Identification Card	80
7.1.1.4	Medical History	80
7.1.1.5	Prior and Concomitant Medications Review	80

7.1.1.5.1	Prior Medications.....	80
7.1.1.5.2	Concomitant Medications	80
7.1.1.6	Assignment of Screening Number	80
7.1.1.7	Assignment of Randomization Number.....	81
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	81
7.1.2	Clinical Procedures/Assessments.....	81
7.1.2.1	Physical Examination.....	81
7.1.2.2	Weight and Height Assessment	81
7.1.2.3	12-Lead ECG	82
7.1.2.4	Vital Signs.....	82
7.1.2.5	Birth Control Confirmation.....	82
7.1.2.6	Adverse Events	82
7.1.2.7	Complete Ocular Examination (for Peg-IFN alfa-2b based Treatment Arm Modification eligibility)	82
7.1.3	Patient-Reported Outcomes (Part B Only)	83
7.1.4	Laboratory Procedures/Assessments	83
7.1.4.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) ..	83
7.1.4.2	Pharmacokinetic/Pharmacodynamic Evaluations	85
7.1.4.2.1	Blood Collection for Pharmacokinetic Sampling	85
7.1.4.3	Future Biomedical Research	87
7.1.4.4	HCV Evaluation.....	88
7.1.4.5	HIV Evaluation (Part B only)	88
7.1.5	Other Procedures.....	89
7.1.5.1	Rescreening.....	89
7.1.5.2	PK Sampling Time Points.....	89
7.1.5.3	Withdrawal/Discontinuation	90
7.1.5.3.1	Withdrawal From Future Biomedical Research	90
7.1.5.4	Blinding/Unblinding	90
7.1.6	Visit Requirements.....	90
7.1.6.1	Screening (Visit 1)	90
7.1.6.2	Study/Treatment Visits	91
7.1.6.3	Drug Administration	91

7.1.6.4	Follow-Up Visits.....	92
7.1.7	Evaluations of Laboratory Safety Signals.....	93
7.1.8	Trial Unblinding.....	94
7.2	Assessing and Recording Adverse Events	94
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor.....	95
7.2.2	Reporting of Pregnancy and Lactation to the Sponsor	95
7.2.3	Immediate Reporting of Adverse Events to the Sponsor	95
7.2.3.1	Serious Adverse Events	95
7.2.3.2	Events of Clinical Interest.....	96
7.2.4	Evaluating Adverse Events	97
7.2.5	Sponsor Responsibility for Reporting Adverse Events	100
7.3	TRIAL GOVERNANCE AND OVERSIGHT	100
7.3.1	Scientific Advisory Committee.....	100
8.0	STATISTICAL ANALYSIS PLAN	100
8.1	Statistical Analysis Plan Summary	100
8.1.1	Efficacy Analyses	100
8.1.2	Safety Analyses.....	101
8.1.3	Power and Sample Size.....	101
8.2	Statistical Analysis Plan	101
8.2.1	Responsibility for Analyses	101
8.2.2	Hypotheses/Estimation	102
8.2.3	Analysis Endpoints	102
8.2.3.1	Efficacy/Pharmacokinetic Endpoints.....	102
8.2.3.1.1	Efficacy Endpoints.....	102
8.2.3.1.2	Pharmacokinetic Endpoints	103
8.2.3.1.3	Exploratory Endpoints	103
8.2.3.2	Safety Endpoints	103
8.2.3.3	Other Endpoints (Part B only)	103
8.2.4	Analysis Populations.....	104
8.2.4.1	Efficacy Analysis Populations	104
8.2.4.2	Safety Analysis Populations	105

8.2.5	Statistical Methods.....	105
8.2.5.1	Statistical Methods for Efficacy Analyses.....	105
8.2.5.2	Statistical Methods for Safety Analyses	107
8.2.5.3	Summaries of Baseline Characteristics, Demographics, and Other Analyses.....	108
8.2.6	Multiplicity	110
8.2.7	Sample Size and Power Calculations.....	110
8.2.7.1	Efficacy Analysis	110
8.2.7.2	Safety Analysis	111
8.2.8	Subgroup Analyses and Effects of Baseline Factors	113
9.0	LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES	113
9.1	Investigational Product	113
9.2	Packaging and Labeling Information	114
9.3	Clinical Supplies Disclosure.....	114
9.4	Storage and Handling Requirements.....	114
9.5	Returns and Reconciliation.....	114
9.6	Standard Policies.....	115
10.0	ADMINISTRATIVE AND REGULATORY DETAILS.....	115
10.1	Confidentiality.....	115
10.1.1	Confidentiality of Data	115
10.1.2	Confidentiality of Subject Records	115
10.1.3	Confidentiality of Investigator Information.....	115
10.2	Compliance with Financial Disclosure Requirements.....	116
10.3	Compliance with Law, Audit and Debarment	116
10.4	Compliance with Trial Registration and Results Posting Requirements	118
10.5	Quality Management System.....	119
10.6	Data Management.....	119
10.7	Publications	119
11.0	LIST OF REFERENCES.....	120
12.0	APPENDICES	127
12.1	Merck Code of Conduct for Clinical Trials.....	127

12.2	Collection and Management of Specimens for Future Biomedical Research.....	129
12.3	Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff	135
12.4	List of Abbreviations and Definitions of Terms.....	146
12.5	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Type.....	148
12.5.1	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Type (Part A)	148
12.5.2	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Type (Part B).....	149
13.0	SIGNATURES.....	150
13.1	Sponsor's Representative	150
13.2	Investigator	150

LIST OF TABLES

Table 1	Subject Populations	15
Table 2	Results of Interferon-free Studies in GT1 Treatment-Naïve Patients	25
Table 3	Summary of Efficacy Results for by Regimen, Genotype, and Presence of Cirrhosis	26
Table 4	Publicly Presented Efficacy Results of Interferon-Free Regimens among G1-Infected Patients Who Failed Prior PR Therapy	28
Table 5	SVR in Co-infected and HCV Monoinfected Subjects	28
Table 6	Part B: Treatment Arms and Durations for Specific Populations.	30
Table 7	Nomenclature for Describing HCV RNA Levels	38
Table 8	Trial Treatments	57
Table 9	Recommended Guidelines for Dose Modification of Ribavirin	59
Table 10	Recommended Guidelines for Dose Modification of Peg-IFN alfa-2b for Treatment Arm Modification Only	59
Table 11	Recommended Dose Reduction (peg-IFN alfa-2b and RBV) for Selected Hematologic and Biochemical Parameters	59
Table 12	Laboratory Tests	84
Table 13	Pharmacokinetic Sampling Timepoints (Part A)	86
Table 14	Pharmacokinetic Sampling Timepoints (Part B)	87
Table 15	Evaluating Adverse Events	98
Table 16	Summary of Analysis Strategy for Key Efficacy Endpoints	100
Table 17	Analysis Strategy for Efficacy Variables	107
Table 18	Analysis Strategy for Safety Parameters	108
Table 19	Two-Sided 95% Confidence Interval for SVR_{12} ; Assuming Various Number of Successes (Per-Protocol Population)	111
Table 20	Upper Bound of the Two-Sided 95% Confidence Interval for the True Proportion of Subjects With an AE	112
Table 21	Probability of Observing Late Transaminase Elevations	112
Table 22	Product Descriptions	113

LIST OF FIGURES

Figure 1	Trial Design for Part A	18
Figure 2	Trial Design for Part B.....	19

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
6.0, 7.1.6.4, 12.5.2	Trial Flow Chart, Follow-Up Visits, Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Type (Part B)	A Follow-Up Week 8 Visit has been added to the study flow chart, Follow-Up visit section, and the table of Approximate Blood Volumes Collected by Trial Visit and Sample Type.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
4.2.3.1.1.2	Definition of Virologic Failure: Futility, Virologic Breakthrough, Rebound, and Relapse	The Futility rule at Treatment Week 4 has been removed from Part B.

Section Number (s)	Section Title(s)	Description of Change (s)
5.5, 5.7	Concomitant Medications (allowed & prohibited), Diet Considerations	Herbal Supplements and Grapefruit Juice have been added as prohibited medications.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-5172 in Combination with MK-8742 +/- RBV
Trial Phase	Phase IIa for Part A and Phase II for Part B
Clinical Indication	Treatment of hepatitis C virus infection
Trial Type	Interventional
Type of control	Part A: Dose response without active control; Part B: No active control and not a dose response study.
Route of administration	Oral
Trial Blinding	Part A: Double-blind Part B: Open-label
Treatment Groups	<p>Part A:</p> <ol style="list-style-type: none"> 1. Treatment Naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 20 mg + RBV 2. Treatment Naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV 3. Treatment Naïve (non-cirrhotic/GT1b only): MK-5172 100 mg + MK-8742 50 mg <p>Part B:</p> <ol style="list-style-type: none"> 1. Treatment Naïve (non-cirrhotic/GT1a only): MK-5172 100 mg + MK-8742 50 mg + RBV for 8 weeks (n=30) 2. Treatment Naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30) 3. Treatment Naïve (non-cirrhotic/GT1a only): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30) 4. Treatment Naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30) 5. Treatment Naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30) 6. Treatment Naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=30) 7. Treatment Naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=30) 8. Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30) 9. Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30) 10. Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=30) 11. Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=30) 12. Treatment Naïve Co-Infected with HIV (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30) 13. Treatment Naïve Co-Infected with HIV (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30)
Number of trial subjects	Approximately 60 subjects will be enrolled in Part A and, for Part B , approximately 390 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 3 months (12 Weeks) of enrollment + 45 days (6.5 Weeks) for screening + up to an additional 48 weeks of treatment/ follow-up for a total of 66.5 weeks for either Part A or Part B from the time the first subject signs the informed

	consent until the last subject's last visit.
Duration of Participation	<p>For Part A: Each subject will participate in the trial for approximately 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. In the case of certain situations of rescue (see Section 5.6) some subjects may require an additional 12 weeks of PR treatment before they enter the follow-up phase for a total of 54.5 weeks in the study.</p> <p>In Part B: After a screening phase of 45 days or 6.5 weeks, subjects will be receiving assigned therapy for approximately 8, 12, or 18 weeks. After the end of treatment, each subject will be followed for 24 weeks for a total of up to 38.5, 42.5, or 48.5 weeks in the study.</p>
Randomization Ratio	<p>For Part A: 2:2:3 ratio to three treatment arms for GT1b subjects and 1:1 ratio to treatment arms 1 and 2 for GT1a subjects.</p> <p>In Part B: <u>Treatment Naïve (Non-cirrhotic: Arms 1-3):</u> GT1a subjects will be randomized to 3 treatment arms in a ratio of 2:1:2 to receive 8 weeks of open label MK-5172 100 mg + MK-8742 50 mg + RBV, or 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV. GT1 non-a subjects will all be allocated to receive 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg + RBV.</p> <p><u>Treatment Naïve (Cirrhotic: Arms 4-7):</u> Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.</p> <p><u>Null-responders (Cirrhotic or Non-cirrhotic: Arms 8-11):</u> Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.</p> <p><u>Treatment Naïve with HIV co-infection (Non-cirrhotic: Arms 12-13):</u> Subjects will be randomized to 2 treatment arms in a ratio of 1:1 to receive 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.</p>

2.0 TRIAL DESIGN

2.1 Trial Design

Note: Please see section 12.4 for lists of abbreviations.

Part A:

This is a randomized, dose-response, parallel-group, multiple-site, double-blind, trial comparing 100 mg of MK-5172 in combination with two doses of MK-8742 +/- ribavirin (RBV) in subjects with chronic hepatitis C virus infection to be conducted in conformance with Good Clinical Practices.

A total of sixty (60) treatment naïve, genotype 1 (GT1), interferon eligible, non-cirrhotic subjects will be studied. Forty-eight (48) subjects will be randomized in a 1:1 ratio to 2 treatment arms in which open label MK-5172 at 100 mg once daily (QD) will be administered concomitantly with blinded MK-8742 doses of either 20 or 50 mg QD, with twice daily (BID) RBV. Subjects in these two arms will be stratified by GT1a vs. GT1b with at least 50% of treatment arms 1 and 2 comprised of GT 1a subjects. A third arm of 12 subjects infected with GT1b will be studied in a regimen of MK-5172 at 100 mg QD with MK-8742 at 50 mg, without RBV. All arms are for a duration of 12 weeks.

For Part B:

An additional 390 subjects, as defined in [Table 1](#), will be randomized to 13 arms. These subjects, who have HCV GT1 and HCV RNA levels of $\leq 10,000$ IU/mL, will be enrolled into this randomized, parallel-group, multiple-site, open-label, trial comparing different subject populations exposed to different durations of treatment with 100 mg of MK-5172 in combination with 50 mg of MK-8742 +/- ribavirin (RBV) in subjects with chronic hepatitis C virus infection.

Subjects enrolled into arms that contain both GT1a vs. GT1 non-a will be distributed such that at least 40% of subjects enrolled in each arm will be GT1a. Additionally, in the subject population of null-responders, arms will be stratified by cirrhotic and non-cirrhotic subjects and the population of null-responders will be composed of at least 70% who are classified as a subject who experienced a <2 log reduction in HCV RNA at TW 12 of a Peg-IFN/RBV regimen. The 4 subject populations are described in [Table 1](#).

Table 1 Subject Populations

Subject Population	Definition of Subject Population ¹	Cirrhosis ² Yes/No	Total n of Population
Treatment naïve (TN) Non-cirrhotic	Subjects are naïve to all anti-HCV treatment, have no evidence of cirrhosis, and are not infected with HIV-1	No	90
Treatment naïve (TN) Cirrhotic	Subjects are naïve to all anti-HCV treatment, have had either a liver biopsy or non-invasive test to diagnose that they are cirrhotic as defined in Section 5.1.2, Subject Inclusion Criteria, and are not infected with HIV-1	Yes	120
Null-Responders Cirrhotic and Non-cirrhotic	Subjects have not previously received any HCV direct-acting antivirals, and have had either a liver biopsy or non-invasive test to diagnose that they are either cirrhotic or non-cirrhotic as defined in Section 5.1.2, Subject Inclusion Criteria, and are not infected with HIV-1. In addition, a null-responder is classified as a subject who experienced a <2 log reduction in HCV RNA at TW 12 of a Peg-IFN/RBV regimen (P/R Null-Responder) OR a <1 log drop at TW 4 and discontinued therapy prior to WK 12 of a Peg-IFN/RBV regimen	Both or Either	120
Treatment naïve (TN) Non-cirrhotic HIV co-infection	Subjects are naïve to all anti-HCV treatment, have no evidence of cirrhosis, and are infected with HIV-1 and have stable HIV-1 infection, defined as: <ul style="list-style-type: none"> Undetectable plasma HIV-RNA for a minimum of 24 weeks prior to study entry (Day 1) and no history of HIV-1 virologic failure for at least 24 weeks prior to Day 1 (AND) On a stable antiretroviral therapy (ART) for at least 8 weeks prior to Day 1 using a dual NRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS raltegravir (RAL). (AND) Subjects CD4+ T-cell count must be >300 cells/mm³ at screening (AND) Has not ever failed more than 1 past HIV treatment regimen 	No	60
¹ Please refer to section 5.1.2, Subject Inclusion Criteria for full definition of each subject population. ² Reference Section 5.1.2, Subject Inclusion Criteria for cirrhosis definitions.			

Treatment Naïve (non-cirrhotic): Arms 1-3

The first population will be composed of 90 treatment naïve (TN), genotype 1 (GT1), non-cirrhotic subjects. GT1a subjects will be randomized to 3 arms in a ratio of 2:1:2 to receive 8

weeks of open label MK-5172 at 100 mg once daily (QD) administered concomitantly with 50 mg of MK-8742 QD and BID RBV, or 12 weeks of open label MK-5172 at 100 mg QD administered concomitantly with 50 mg of MK-8742 QD, with or without BID RBV. GT 1 non-a subjects will all be allocated to 12 weeks of open label MK-5172 at 100 mg QD administered concomitantly with 50 mg of MK-8742 QD, with BID RBV.

Treatment Naïve (cirrhotic): Arms 4-7

An additional 120 TN, GT1 cirrhotic subjects, will be randomized to arms in a 1:1:1:1 ratio to receive 12 or 18 weeks of open label MK-5172 at 100 mg once daily (QD) administered concomitantly with 50 mg of MK-8742 QD, with or without twice daily (BID) RBV.

Null-responders (cirrhotic and non-cirrhotic): Arms 8-11

An additional 120 GT1, subjects (cirrhotic and non-cirrhotic) who are null-responders to prior Peg-IFN/RBV therapy, will be randomized in a 1:1:1:1 ratio to receive 12 or 18 weeks of open label MK-5172 at 100 mg once daily (QD) administered concomitantly with 50 mg of MK-8742 QD with or without twice daily (BID) RBV.

Treatment Naïve with HIV co-infection (non-cirrhotic): Arms 12-13

Finally, an additional 60 TN, GT1, non-cirrhotic subjects with HIV co-infection, will be randomized in a 1:1 ratio to receive 12 weeks of open label MK-5172 at 100 mg once daily (QD) administered concomitantly with 50 mg of MK-8742 QD, with or without twice daily (BID) RBV.

After a maximum 45 day screening window, randomized subjects in each treatment arm will receive either 8, 12 or 18 weeks of therapy and be followed for 24 weeks of follow-up for up to a total of about 39, 43 or 49 weeks in the study, depending on their duration of therapy.

Part A and Part B:

During the course of the trial, there will be periodic analyses conducted to evaluate safety and efficacy. The purpose of these analyses is for planning the next phase of program development.

Subjects should be discontinued from all study therapy (where applicable) if they meet any of the criteria for discontinuation of therapy described in Section 5.8.

In Part A of the study, a subject who meets the criteria for virologic failure or discontinues study medications due to safety concerns that are not attributed to RBV will be offered optional rescue therapy as described in Section 5.6. **In Part B** of this study, the Sponsor will not provide any rescue therapy.

In Part A and Part B, as described in Section 5.6, should any treatment arm in the study present with an unacceptable relapse rate, it will be recommended that the remaining subjects in that treatment arm, regardless of where they are in their regimen, have Peg-IFN alfa-2b added (and RBV added in the RBV free arms) through the remaining weeks of therapy. In addition, their treatment will be extended to include an additional 12 weeks of Peg-IFN alfa-2b + RBV (treatment arm modification).

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 for Part A is depicted in [Figure 1](#).

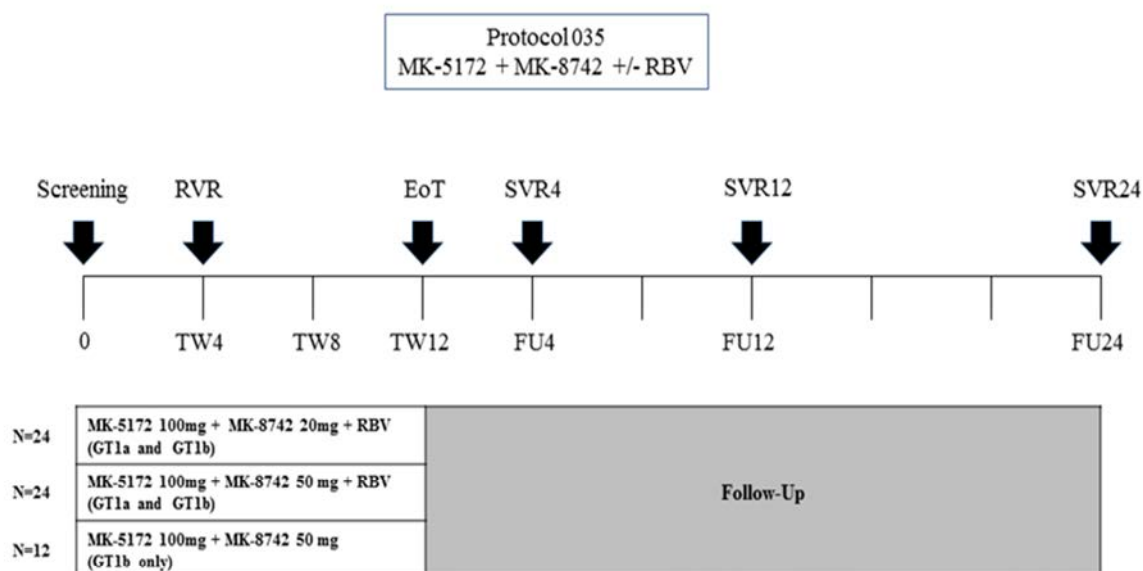


Figure 1 Trial Design for Part A

The trial design for Part B is depicted in Figure 2.

Treatment Naïve; Non-Cirrhotic						
n	Baseline	WK4	WK 8	WK12	WK18	WK32/36/42
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 1 GT 1a only
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 2 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 3 GT 1a only
Treatment Naïve; Cirrhotic						
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 4 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 5 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 6 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 7 GT1a/non-a
Null-Responders; Cirrhotic and Non-Cirrhotic						
A Null-Responder is classified as a subject who experienced a <1 log drop at TW 4 or a <2 log drop at TW 12 when previously treated with P/R						
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 8 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 9 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 10 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 11 GT1a/non-a
Treatment Naïve Co-Infected with HIV; Non-Cirrhotic						
30	MK-5172 100 mg+MK-8742 50 mg+RBV			24 Week Follow-Up		
						Arm 12 GT1a/non-a
30	MK-5172 100 mg+MK-8742 50 mg			24 Week Follow-Up		
						Arm 13 GT1a/non-a

Indicates RBV Free Arm

Figure 2 Trial Design for Part B

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

The following applies to Part A and Part B (unless otherwise specified):

As this is a hypothesis-generating study, there are no formal hypotheses for this study.

In subjects with chronic HCV GT1 infection with pre-treatment HCV RNA of at least 10,000 IU/mL:

The Primary Objective(s) are:

- (1) **Objective:** To evaluate the efficacy of each treatment arm of MK-5172 in combination with MK-8742 +/- RBV 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 <25 IU/mL (either TD(u) or TND) 12 weeks after the end of all study therapy.
- (2) **Objective:** To evaluate the safety and tolerability of MK-5172 in combination with MK-8742 +/- RBV.

Note: For Part B, each treatment arm will be assessed for efficacy, safety, and tolerability (as defined above) within each subject population.

3.2 Secondary Objective(s) & Hypothesis(es)

The following applies to Part A and Part B (unless otherwise specified):

In subjects with chronic HCV GT1 infection with pre-treatment HCV RNA of at least 10,000 IU/mL:

- (1) **Objective:** To evaluate the efficacy of each treatment arm of MK-5172 in combination with MK-8742 +/- RBV as assessed by the time to first achievement of undetectable (TND) HCV RNA.
- (2) **Objective:** To evaluate the efficacy of each treatment arm of MK-5172 in combination with MK-8742 +/- RBV as assessed by the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA <25 IU/mL at Week 2, 4, and end of treatment visit for the 8 and 12 Week duration arms and, Week 2, 4, 12, and end of treatment visit for the 18 Week duration arm.

Note: In the 12 Week treatment duration arms, Week 12 and the End of Treatment Visit may be the same.

- (3) **Objective:** To evaluate the efficacy of each treatment arm of MK-5172 in combination with MK-8742 +/- RBV as assessed by the proportion of subjects achieving:
- SVR₄ (Sustained Virologic Response 4 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 4 weeks after the end of all study therapy.
 - SVR₂₄ (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 24 weeks after the end of all study therapy.
- (4) **Objective:** To evaluate the emergence of viral resistance-associated variants (RAVs) resistant to MK-5172 and MK-8742 when administered as part of a combination regimen +/- RBV.

In Part B, the secondary objectives above will be evaluated within each subject population separately. In addition, the following objectives will also be evaluated for the HIV co-infected population:

- (5) **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 (only applicable for co-infected sub-population in part B of the study)
- (6) **Objective:** To evaluate the effect of the study regimen on CD4+ T-cell counts (only applicable for co-infected sub-population in part B of the study)

3.3 Exploratory Objectives

The following applies to Part A and Part B (unless otherwise specified):

- (1) **Objective:** To evaluate the pharmacokinetics (PK) of MK-5172, MK-8742, and RBV.
- (2) **Objective:** To evaluate the pharmacokinetic/pharmacodynamics (PK/PD) relationship which may include MK-5172, MK-8742, and RBV.
- (3) **Objective:** To assess the genetic variation in the human *IL28B* gene as a predictor of virologic response in each treatment arm.
- (4) **Objective:** To evaluate biomarkers (e.g., proteins, RNA expression (Part A only), and metabolite production), that may be predictive of tolerability of study drugs and virologic response to MK-5172 in combination with MK-8742 +/- RBV by comparing biomarker levels over time in subjects who respond or fail study therapy.
- (5) **Objective:** To describe changes from baseline in health-related quality of life during and after treatment with MK-5172 and MK-8742 (only applicable for Part B)

- (6) **Objective:** To assess the association between baseline CD4+ T-cell count and achieving HCV SVR₁₂ for HIV co-infected subjects (only applicable for co-infected sub-population in part B of the study).

Note: For Part B, applicable treatment arms will be assessed for the exploratory objectives (defined above) for each subject population.

4.0 BACKGROUND & RATIONALE

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

03SRGX

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with CHC genotype 1 virus infection 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:

In Part A:

1. be 18 years of age on day of signing informed consent.
2. have a body weight 50 kg (111 lbs) and 125 kg (275 lbs).
3. have chronic, compensated HCV GT 1a or GT 1b infection:
 - Positive serology for HCV with HCV RNA levels 10,000 IU/mL in peripheral blood at screening, and
 - Absence (no medical history or physical findings) of ascites, bleeding esophageal varices, hepatic encephalopathy, or other signs or symptoms of advanced liver disease, or cirrhosis
4. have had a liver biopsy without evidence of advanced fibrosis, cirrhosis and/or hepatocellular carcinoma. A liver biopsy done prior to screening is acceptable if it is performed:
 - Within 2 years of screening and the result was METAVIR (or equivalent) Stage 0 (F0) to 2 (F2).

If the prior liver biopsy was obtained outside the acceptable windows, a repeat biopsy may be performed, and the results must show no evidence of advanced fibrosis, cirrhosis and/or hepatocellular carcinoma in order for the subject to be randomized in the study.

For countries where liver biopsy is not performed prior to treatment and where noninvasive tests (for e.g. FibroScan and/or FibroSure®) are used for staging of liver disease, these results may be used to assess eligibility. Subjects with a documented FibroScan score of 9.5 kPa, or FibroSure® of 0.58, are allowed to be enrolled in the study. These non-invasive tests done prior to screening are acceptable if they were performed within 1 year of screening and meet the indicated cut-offs. If the prior non-invasive tests were not performed within 1 year of screening, results from one of these non-invasive tests are required before study drug dosing. If a subject has both liver biopsy and one of these non-invasive tests, whichever test demonstrates the presence of advanced fibrosis or cirrhosis would be used to determine eligibility. In other words, if the liver biopsy shows advanced fibrosis or cirrhosis, the subject is excluded, regardless of results of the non-invasive assay. If the liver biopsy does not show advanced fibrosis or cirrhosis, but the non-invasive assay does, then the subject is excluded as well.

5. agree to use two acceptable methods of birth control from at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug, or longer if dictated by local regulations (for female subject who is of childbearing potential or male subject with female sexual partner who is of childbearing potential).

If acceptable by local regulatory agencies, methods of birth control allowed in the study are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, female condom, male condom with spermicide, vasectomy, and true abstinence: Abstinence is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal method, use of post-ovulation methods) and withdrawal are not acceptable methods of contraception].

For the purposes of this protocol, a woman of non-childbearing potential is defined as one who has either 1) reached natural menopause (defined as 12 months with no menses without an alternative medical cause), 2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.

For the purposes of this protocol, a male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

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

For Part B:

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

1. be 18 years of age on day of signing informed consent.
2. have a body weight 50 kg (111 lbs) and 125 kg (275 lbs).
3. have chronic, compensated HCV GT1 infection:
 - Positive for anti-HCV antibody, HCV RNA, or an HCV genotype at least 6 months before screening, and positive for HCV RNA (10,000 IU/mL in peripheral blood)
 - Absence (no medical history or physical findings) of ascites, bleeding esophageal varices, hepatic encephalopathy, or other signs or symptoms of advanced liver disease

4. have liver disease staging assessment as follows:

Cirrhosis is defined as any one of the following [53,54]:

- 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 [54]*
- 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: $\text{AST} \div \text{lab upper limit of normal (ULN) for AST} \times 100 \div \{\text{platelet count} \div 100\}$ (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[54]*
- 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 criteria, a liver biopsy is required. Liver biopsy results supersede the results obtained by Fibroscan or FibroSure®.

5. Have prior Peg-IFN treatment status as follows:

- Treatment naïve: Naive to all anti-HCV treatment
- PegIFN/Ribavirin (P/R) Null Responders: Subjects in this category can be further defined as:
 - P/R Null responder: <2 log₁₀ IU/mL reduction in HCV RNA at Week 12 of a Peg-IFN/RBV regimen
 - OR
 - <1 log₁₀ IU/mL decline from baseline at Week 4 futility rule and discontinued therapy prior to Week 12 of a Peg-IFN/RBV regimen

6. For HIV coinfecting subjects these additional criteria must also be met:

- 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.

- Be on stable HIV Antiretroviral Therapy (ART) for at least 8 weeks prior to study entry using a dual NRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS raltegravir. Subjects on ART should plan to remain on the same therapy for at least 12 weeks after Day 1.
 - CD4+ T-cell count > 300 cells/mm³ at screening.
 - Have undetectable plasma HIV-1 RNA at screening and history of having achieved undetectable (i.e., below the limit of assay detection) plasma HIV-1 RNA by any FDA-approved test for quantifying HIV-1 RNA at any laboratory that has a CLIA certification or its equivalent, and no history of 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) for at least 24 Weeks prior to study entry
 - Has not ever failed more than 1 past HIV treatment regimen
7. Agree to 2 acceptable methods of birth control from at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug, or longer if dictated by local regulations (for female subject who is of childbearing potential or male subject with female sexual partner who is of childbearing potential).

If acceptable by local regulatory agencies, methods of birth control allowed in the study are: intrauterine device (IUD), diaphragm with spermicide, hormonal contraceptives (e.g., birth control pills, transdermal patch, or injectables), contraceptive sponge, female condom, male condom with spermicide, vasectomy, and true abstinence: Abstinence is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal method, use of post-ovulation methods) and withdrawal are not acceptable methods of contraception]. True abstinence does not require a second method of birth control.

For the purposes of this protocol, a woman of non-childbearing potential is defined as one who has either 1) reached natural menopause (defined as 12 months with no menses without an alternative medical cause), 2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.

For the purposes of this protocol, a male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

8. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
9. The subject may also provide consent/assent 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:

For Part A:

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 a non-GT 1 HCV infection, including a mixed GT infection (with a non-GT 1) or a non-typeable genotype.
3. is NOT treatment naïve, i.e. subject has had previous treatment with any interferon, RBV, approved or experimental direct acting antiviral(s), or other investigational therapies for HCV.
4. is determined by documented records, to be HIV positive or is known to be coinfecting with hepatitis B virus (HBsAg positive).
5. has evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC.
6. is taking or plans to take any of the following medications:
 - 6.1. Significant inducers or inhibitors of CYP3A4 substrates 2 weeks prior to start of study medications (see Prohibited Medications, Section 5.5 for further guidance).
 - 6.2. Herbal supplements, including but not limited to St. John's Wort (*Hypericum perforatum*) 2 weeks prior to start of study medications (Day 1). Only silymarin (Milk Thistle, *Silybum marianum*) is permitted during the trial.
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 study. Collection of additional blood, urine, or tissue samples or additional data, beyond that specified in this protocol, is prohibited (other than that related to subject's medical care).
8. is diabetic and/or hypertensive with clinically significant ocular examination findings: retinopathy, cotton wool spots, optic nerve disorder, retinal hemorrhage, or any other clinically significant abnormality.

9. has pre-existing psychiatric condition(s) including but not limited to:
 - 9.1. Current moderate or severe depression.
 - 9.2. History of depression associated with any of the following:
 - 9.2.1. Hospitalization for depression.
 - 9.2.2. Electroconvulsive therapy for depression.
 - 9.2.3. Depression that resulted in a prolonged absence from work and/or significant disruption of daily functions.
 - 9.3. Suicidal or homicidal ideation and/or attempt.
 - 9.4. History of severe psychiatric disorders (including but not limited to schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, or mania).
 - 9.5. Past history or current use of lithium.
 - 9.6. Past history or current use of antipsychotic drugs for those conditions listed in Exclusion Criterion 9.4.
10. has a clinical diagnosis of substance abuse of the following specified drugs within specified timeframes:
 - 10.1. alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over-the-counter drugs: within 1 year of the screening visit OR
 - 10.2. multi-drug abuse (e.g., two or more of the substances listed in Exclusion Criterion 10.1): within 1 years of screening visit OR
 - 10.3. receiving opiate agonist substitution therapy within 1 year of screening visit.
 - 10.4. historic marijuana use is deemed excessive by a physician investigator or is interfering with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must be instructed to discontinue any current use of recreational marijuana prior to entry into trial and throughout the trial period.
11. has any known medical condition that could interfere with the subject's participation in and completion of the trial, including, but not limited to:
 - 11.1. Central nervous system (CNS) trauma requiring intubation, intracranial pressure monitoring, brain meningeal or skull surgery, or resulting in seizure, coma, permanent neurologic deficits, abnormal brain imaging, or cerebral spinal fluid

- (CSF) leak. Prior brain hemorrhage and/or intracranial aneurysms (whether adequately repaired or not).
- 11.2. Current or history of seizure disorder unless seizure was >10 years ago, a single isolated event, no anti-seizure medications prescribed, and a normal neurological examination is documented in trial files within 6 months of Day 1.
 - 11.3. History of stroke or transient ischemic attack.
 - 11.4. Immunologically mediated disease (e.g., inflammatory bowel disease [Crohn's disease, ulcerative colitis], celiac disease, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, sarcoidosis, severe psoriasis requiring oral or injected treatment, or symptomatic thyroid disorder).
 - 11.5. Chronic pulmonary disease (e.g., clinical chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, sarcoidosis). Subjects with symptoms of chronic pulmonary disease should have a chest x-ray prior to inclusion to rule out conditions that may interfere with Peg-IFN (rescue therapy only).
 - 11.6. Current or history of any clinically significant cardiac abnormalities/dysfunction (e.g., angina, congestive heart failure, myocardial infarction, pulmonary hypertension, complex congenital heart disease, cardiomyopathy, significant arrhythmia) including current uncontrolled hypertension, history of use of antianginal agents for cardiac conditions, or clinically significant abnormality on ECG performed at the pre-study screening visit.
 - 11.7. Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the trial.
 - 11.8. Active clinical gout within the last year.
 - 11.9. Hemoglobinopathy, including, but not limited to, thalassemia major.
 - 11.10. Myelodysplastic syndromes.
 - 11.11. Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.
 - 11.12. Poor venous access that precludes routine peripheral blood sampling required for this trial.
 - 11.13. Subject with indwelling venous catheters.
 - 11.14. Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).

- 11.15. Severe concurrent disease such as chronic renal disease.
- 11.16. Other serious medical condition which could be exacerbated by Peg-IFN alfa-2b and/or RBV, in the opinion of the investigator.
12. has evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years (except adequately treated carcinoma in situ and basal cell carcinoma of the skin). Subjects under evaluation for malignancy are not eligible.
13. (female) is pregnant, lactating, expecting to conceive or donate eggs, or is of childbearing potential and unwilling to commit to two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criterion #5); or male subject is planning to impregnate or provide sperm donation or has a female sexual partner of childbearing potential and is unwilling to commit to using a two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criterion #5).
14. is a male whose female partner is/are pregnant (this is a contraindication for RBV use).
15. has any other condition which, in the opinion of the principal investigator or study physician, would make the subject unsuitable for enrollment or could interfere with the subject participating in and completing the study.
16. had a life-threatening SAE during the screening period.
17. is a member or a family member of the investigational study staff or sponsor staff directly involved with this study.
18. 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, can be enrolled.

19. has exclusionary laboratory values as listed below:

Note: If any of the laboratory exclusion criteria are met, the site may have the subject retested. If a single value is within 10% of the listed laboratory exclusion criterion value, and the value is considered not clinically significant by the investigator, the subject may be considered for enrollment.

- 19.1. Hematologic, biochemical, and serologic criteria (growth factors may not be used to achieve study entry requirements):

19.1.1. Hemoglobin <12 g/dL for females and <13 g/dL for males.

19.1.2. Neutrophils <1.5 x 10³/μL (<1.2 x 10³/μL for Blacks).

- 19.1.3. Platelets $<150 \times 10^3/\mu\text{L}$ [A subject is excluded if this criteria is met; no retests can be performed and ranges (for e.g. within 10% of exclusion criterion value) cannot be utilized].
- 19.1.4. Direct bilirubin $>1.5 \times \text{ULN}$ (upper limit of normal) of the laboratory reference range. Total bilirubin $>1.6 \text{ mg/dL}$ unless history of Gilbert's disease. If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart.
- 19.2. Serum albumin $< \text{LLN}$ (lower limit of normal) of laboratory reference range.
- 19.3. Thyroid-stimulating hormone (TSH) $> 1.2 \times \text{ULN}$ or $< 0.8 \times \text{LLN}$ of laboratory reference range with the following exceptions:
 - 19.3.1. The subject may be enrolled if clinically euthyroid, AND
 - 19.3.2. The euthyroid function is confirmed by T3/T4 testing.
- 19.4. Serum creatinine $> \text{ULN}$ of the laboratory reference.
- 19.5. Creatinine clearance $<50 \text{ mL/min}$
- 19.6. Serum glucose:
 - 19.6.1. For subjects not previously diagnosed with diabetes mellitus;
 - 19.6.1.1. ULN (fasting) unless HbA1c $\geq 7\%$.
 - 19.6.2. For subjects previously diagnosed with diabetes mellitus, HbA1c $> 8.5\%$.
- 19.7. PT/PTT values $> 10\%$ above laboratory reference range.
- 19.8. Anti-nuclear antibodies (ANA) $> 1:320$
- 19.9. ALT $> 350 \text{ IU/L}$
- 19.10. AST $> 350 \text{ IU/L}$

In Part B:

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 a non-GT1 HCV infection, including mixed GT infection (with a non-GT 1) or a non-typeable genotype.
3. Has previously received any HCV direct-acting antivirals.

4. Evidence of decompensated liver disease manifested by the presence of or history of ascites, variceal bleeding, or hepatic encephalopathy. If hepatic cirrhosis is determined by liver biopsy (Stage 4 Metavir or Stage 5, 6 Ishak) or by imaging, then participants must be no more than Child-Pugh Class A and have a Child-Pugh-Turcotte (CPT) score of 6 or less.

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

5. Is determined to be HIV positive (N/A for study arm 12 and 13) and is determined to be coinfectd with hepatitis B virus (e.g. HBsAg positive)
6. has evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC.
7. is taking or plans to take any of the prohibited medications listed in Section 5 of this protocol within 2 weeks of Day 1.
8. 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 study. Collection of additional blood, urine, or tissue samples or additional data, beyond that specified in this protocol, is prohibited (other than that related to subject's medical care).
9. has a clinical diagnosis of substance abuse of the following specified drugs within specified timeframes:
 - alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over-the-counter drugs: within 1 year of the screening visit or, if shorter is judged by the investigator to be capable of complying with study procedures, OR receiving opiate agonist substitution therapy within 1 year of screening visit or, if shorter is judged by the investigator to be capable of complying with study procedures, OR
 - historic marijuana use is deemed excessive by a physician investigator or is interfering with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must be instructed to discontinue any current use of recreational marijuana prior to entry into trial and throughout the trial period.
10. has evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years (except adequately treated carcinoma in situ, squamous cell skin cancer, and basal cell carcinoma of the skin). Subjects under evaluation for malignancy are not eligible.
11. (female) is pregnant, lactating, expecting to conceive or donate eggs, or is of childbearing potential and unwilling to commit to two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criterion #5); or male subject is

planning to impregnate or provide sperm donation or has a female sexual partner of childbearing potential and is unwilling to commit to using a two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criterion #5).

12. is a male whose female partner is/are pregnant (this is a contraindication for RBV use).
13. has any other condition which, in the opinion of the principal investigator or study physician, would make the subject unsuitable for enrollment or could interfere with the subject participating in and completing the study, including but not limited to:
- 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 indwelling venous catheters.
 - Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).
 - Hemoglobinopathy, including, but not limited to, thalassemia major.
 - Current or history of any clinically significant cardiac abnormalities/dysfunction (e.g., angina, congestive heart failure, myocardial infarction, pulmonary hypertension, complex congenital heart disease, cardiomyopathy, significant arrhythmia) including current uncontrolled hypertension, history of use of antianginal agents for cardiac conditions, or clinically significant abnormality on ECG performed at the pre-study screening visit.
 - Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the trial.
14. had a life-threatening SAE during the screening period.
15. is a member or a family member of the investigational study staff or sponsor staff directly involved with this study.
16. 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, can be enrolled.

17. For subjects diagnosed with diabetes mellitus, chart documented HbA1c >8.5% to exclude uncontrolled diabetics

18. has exclusionary laboratory values as listed below:

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

Laboratory Assessment	Patient Population	
	Noncirrhotic	Cirrhotic
creatinine clearance	<50 mL/min	<50 mL/min
hemoglobin	< LLN (lower limit of normal) of laboratory reference range	< LLN (lower limit of normal) of laboratory reference range
neutrophils	<1.5 x 10 ³ /μL (<1.2 x 10 ³ /μL for Blacks)	<1.5 x 10 ³ /μL (<1.2 x 10 ³ /μL for Blacks)
platelets	<125 x 10 ³ /μL	<70 x 10 ³ /μL
direct bilirubin	>1.5 x ULN	>1.5 x ULN
Total Bilirubin	>1.6 mg/dL unless history of Gilbert's disease. (If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart)	>2.0 mg/dL unless history of Gilbert's disease. (If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart)
Serum Albumin	< 3.5 g/dL (lower limit of normal) of laboratory reference range	< 3.0 g/dL (lower limit of normal) of laboratory reference range
INR	>1.5	>1.7
ALT	>350	>350
AST	>350	>350
AFP	≥100ng/mL	≥100ng/mL

Prior to administering Peg-IFN (for Treatment Arm Modification only), these additional criteria are exclusionary and must be evaluated;

19. is diabetic and/or hypertensive with clinically significant ocular examination findings: retinopathy, cotton wool spots, optic nerve disorder, retinal hemorrhage, or any other clinically significant abnormality.

20. In addition to lab criteria in Exclusion Criteria 18, has exclusionary laboratory values as listed below:

Laboratory Assessment	Patient Population	
	Noncirrhotic	Cirrhotic
TSH	> 1.2 x ULN or < 0.8 x LLN of laboratory reference range with the following exceptions: The subject may be enrolled if clinically euthyroid, AND The euthyroid function is confirmed by T3/T4 testing.	> 1.2 x ULN or < 0.8 x LLN of laboratory reference range with the following exceptions: The subject may be enrolled if clinically euthyroid, AND The euthyroid function is confirmed by T3/T4 testing.
Serum creatinine	>ULN of the laboratory reference	>ULN of the laboratory reference
Fasting Serum glucose	For subjects not previously diagnosed with diabetes mellitus : \geq ULN (fasting) unless HbA1c \leq 7%. For subjects previously diagnosed with diabetes mellitus, HbA1c > 8.5%	For subjects not previously diagnosed with diabetes mellitus : \geq 140 mg/dL nonfasting unless HbA1c \leq 7% OR \geq 100 mg/dL fasting unless HbA1c \leq 7%. For subjects previously diagnosed with diabetes mellitus, HbA1c > 8.5%
Anti-nuclear antibodies (ANA)	>1:320	>1:320

21. has pre-existing psychiatric condition(s) including but not limited to:

- Current moderate or severe depression.
- History of depression associated with any of the following:
 - Hospitalization for depression.
 - Electroconvulsive therapy for depression.
 - Depression that resulted in a prolonged absence from work and/or significant disruption of daily functions.
- Suicidal or homicidal ideation and/or attempt.
- History of severe psychiatric disorders (including but not limited to schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, or mania).
- Past history or current use of lithium.
- Past history or current use of antipsychotic drugs for those conditions listed in Exclusion Criterion 21.

22. has any known medical condition that could interfere with the subject's participation in and completion of the trial, including, but not limited to:

- Other serious medical condition which could be exacerbated by Peg-IFN alfa-2b in the opinion of the investigator.
- Central nervous system (CNS) trauma requiring intubation, intracranial pressure monitoring, brain meningeal or skull surgery, or resulting in seizure, coma, permanent neurologic deficits, abnormal brain imaging, or cerebral spinal fluid (CSF) leak. Prior brain hemorrhage and/or intracranial aneurysms (whether adequately repaired or not).
- Current or history of seizure disorder unless seizure was >10 years ago, a single isolated event, no anti-seizure medications prescribed, and a normal neurological examination is documented in trial files within 6 months of Day 1.
- History of stroke.
- Immunologically mediated disease (e.g., inflammatory bowel disease [Crohn's disease, ulcerative colitis], celiac disease, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, sarcoidosis, severe psoriasis requiring oral or injected treatment, or symptomatic thyroid disorder.
- Chronic pulmonary disease (e.g., clinical chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, sarcoidosis). Subjects with symptoms of chronic pulmonary disease should have a chest x-ray prior to inclusion to rule out conditions that may interfere with Peg-IFN
- Active clinical gout within the last year.
- Myelodysplastic syndromes.
- Severe concurrent disease such as chronic renal disease.

5.2 Trial Treatments

Treatments to be used in this trial are outlined below in [Table 8](#).

For Part A:

Table 8 Trial Treatments

Drug	Weight	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-5172	N/A	100 mg	QD	Oral	12 Weeks	experimental
MK-8742	N/A	20 or 50 mg ⁴	QD	Oral	12 Weeks	experimental
Placebo to MK-8742 (Part A only)	N/A	N/A	QD	Oral	12 Weeks	placebo-comparator
RBV ¹ (Rebetol™), 200 mg capsules	50 kg	800 mg (2 in AM, 2 in PM)	BID	Oral	12 Weeks	Experimental and Treatment Arm Modification
	51-65 kg (112-144 lbs.)	800 mg (2 in AM, 2 in PM)				
	66-80 kg (145-177 lbs.)	1000 mg (2 in AM, 3 in PM)				
	81-105 kg (178-231 lbs.)	1200 mg (3 in AM, 3 in PM)				
	106-125 kg (232-275 lbs.)	1400 mg (3 in AM, 4 in PM)				
Peg-IFN alfa-2b ² (PegIntron™) (Part A only)	51-60 kg (112-133 lbs.)	80 µg (using 80 µg/0.5mL REDIPEN or vial strength)	Once Weekly	Subcutaneous injection	Add on therapy in first 12 weeks + 12 weeks additional	Treatment Arm Modification
	61-75 kg (134-166 lbs.)	96 µg (using 120µg/0.5mL REDIPEN or vial strength)				
	76-85 kg (167-187 lbs.)	120 µg (using 120µg/0.5mL REDIPEN or vial strength)				
	86-105 kg (188-231 lbs.)	150 µg (using 150µg/0.5mL REDIPEN or vial strength)				
	>105-125 kg (>231-275 lbs.)	TBD ³				

¹ In RBV containing arms and in RBV free arms for treatment arm modification (See Section 5.6) of all subjects in combination with MK-5172 and MK8742/placebo through 12 weeks of dosing and in combination with Peg-IFN for an additional 12 weeks

² To be used only when Treatment arm modification is initiated (see Section 5.6).

³ To be determined at time of study entry: For subjects weighing > 105 kg (> 231 lbs), the PegIntron™ dose of 1.5 µg/kg/week should be calculated based on the individual subject weight. Two vials of PegIntron™ may be necessary to provide the dose.

⁴ 20 mg dose of MK-8742 is only applicable for Part A of study

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.

In Part B:

MK-5172 and MK-8742

Subjects will be randomized to receive MK-5172 100 mg QD orally administered concomitantly with MK-8742 50 mg QD orally with or without RBV for 8, 12, or 18 weeks. Drug will be supplied once monthly in a bottle(s). Subjects will be instructed to take their daily medication as instructed on the bottle label(s).

Ribavirin

RBV (Rebetol™) will be administered BID orally (in RBV containing arms) at a total daily dose of 800 mg to 1400 mg based on subject weight on Day 1 (Refer to [Table 8](#) in Section 5.2).

5.2.1 Dose Selection/Modification (Part A and Part B)

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0-Background and Rationale.

Dose Modification

Protocol Regimens:

Dose modification of MK-5172 and MK-8742 is **not** permitted.

If severe adverse events or laboratory abnormalities develop during the study, RBV can be modified based on the recommended guidelines provided in [Table 9](#).

Treatment Arm Modification:

If severe adverse events or laboratory abnormalities develop while a subject is receiving therapy during Treatment Arm Modification, Peg-IFN alfa-2b/RBV, can be modified based on the recommended guidelines provided in [Table 10](#).

Table 9 Recommended Guidelines for Dose Modification of Ribavirin

Body Weight on Day 1	Full Daily Dose (mg/day)	1 st RBV Dose Reduction		2 nd RBV Dose Reduction		3 rd RBV Dose Reduction	
		Dose (mg/day)	Number of 200-mg RBV Capsules	Dose (mg/day)	Number of 200-mg RBV Capsules	Dose (mg/day)	Number of 200-mg RBV Capsules
51 to 65 kg (112 to 144 lb)	800	600	1 in AM/ 2 in PM	400	1 in AM/ 1 in PM	200	1 in PM
66 to 80 kg (145 to 177 lb)	1000	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM	400	1 in AM/ 1 in PM
81 to 105 kg (178 to 231 lb)	1200	1000	2 in AM/ 3 in PM	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM
>105 to 125 kg (232 to 275 lb)	1400	1000	2 in AM/ 3 in PM	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM

Table 10 Recommended Guidelines for Dose Modification of Peg-IFN alfa-2b for Treatment Arm Modification Only

1 st Dose Reduction to PegIntron™ 1.0 µg/kg				2 nd Dose Reduction to PegIntron™ 0.5 µg/kg			
Body Weight on Day 1	PegIntron™ REDIPEN™/Vial Strength to Use	Amount of PegIntron™ (µg) to Administer	Volume (mL) of PegIntron™ to Administer	Body Weight on Day 1	PegIntron™ REDIPEN™/Vial Strength to Use	Amount of PegIntron™ (µg) to Administer	Volume (mL) ² of PegIntron™ to Administer
50 to 60 kg (112 to 133 lb)	50 µg per 0.5 mL	50	0.5	50 to 60 kg (112 to 133 lb)	50 µg per 0.5 mL	30	0.3
61 to 75 kg (134 to 166 lb)	80 µg per 0.5 mL	64	0.4	61 to 75 kg (134 to 166 lb)	50 µg per 0.5 mL	35	0.35
76 to 85 kg (167 to 187 lb)	80 µg per 0.5 mL	80	0.5	76 to 85 kg (167 to 187 lb)	50 µg per 0.5 mL	45	0.45
86 to 104 kg (188 to 230 lb)	120 µg per 0.5 mL	96	0.4	86 to 104 kg (188 to 230 lb)	50 µg per 0.5 mL	50	0.5
105 to 125 kg (231 to 275 lb)	120 µg per 0.5 mL	108	0.45	105 to 125 kg (231 to 275 lb)	80 µg per 0.5 mL	64	0.4

¹ Must use vial. Minimum delivery for REDIPEN™ is 0.3 mL.
² When reconstituted as directed.

Table 11 provides recommended dose reduction of peg-IFN (Treatment Arm Modification Only) and RBV for selected hematologic and biochemical parameters per product labeling.

Table 11 Recommended Dose Reduction (peg-IFN alfa-2b and RBV) for Selected Hematologic and Biochemical Parameters

Parameter	Dose Reduction of peg-IFN alfa-2b or RBV	Discontinuation or Interruption ¹ of peg-IFN alfa-2b and/or RBV
Hemoglobin	< 10 g/dL (RBV)	< 8.5 g/dL (RBV)
White Blood Cell Count	< 1.5 x 10 ⁹ /L (peg-IFN alfa-2b)	< 1.0 x 10 ⁹ /L (peg-IFN alfa-2b)
Neutrophil Count	< 0.75 x 10 ⁹ /L (peg-IFN alfa-2b)	< 0.5 x 10 ⁹ /L (peg-IFN alfa-2b)
Platelet Count	< 50 x 10 ⁹ /L (peg-IFN alfa-2b)	< 25 x 10 ⁹ /L (peg-IFN alfa-2b)
Creatinine		> 2.0 mg/dL (> 176.8 µmol/L) (RBV)
ALT/AST		See Section 5.8 on Withdrawal/Discontinuation

¹ Individual study drug regimen interruptions are permissible based on the results of abnormal laboratory parameters. Treatment interruptions should not exceed 2 consecutive weeks in duration.
ALT = Alanine aminotransferase; AST = Aspartate aminotransferase;
ULN – Upper limit of normal.

Protocol Regimens and Treatment Arm Modification:

The subject should return for assessment at a recommended interval of every week until the AE resolves or the subject is stable. If further dose reduction is required, the second (or third for RBV) level of dose reduction may be used. If the AE persists but does not fall into the range for discontinuation/treatment interruption, the reduced dose may be continued. At the discretion of the physician, doses may be increased to the full dose or directly in steps when the AE subsides.

If for any reason either MK-5172 or MK-8742 needs to be interrupted it can be interrupted for up to 3 days. If either MK-5172 and/or MK-8742 is interrupted for more than 3 days, dosing should be discontinued.

If for any reason RBV needs to be interrupted (e.g. for safety reasons), if possible, it should be restarted within 3 days.

5.2.2 Timing of Dose Administration

MK-5172, MK-8742, and RBV

For Part A:

Subjects will be instructed to take MK-5172, MK-8742 (or placebo), and RBV (in RBV containing arms) orally, in the morning. RBV should be taken with food. A second daily dose of RBV should be taken by itself, with food, in the evening.

In Part B:

Subjects will be instructed to take MK-5172 and MK-8742 together without regard to food in the morning. Subjects taking RBV will take one dose in the morning and one dose in the evening. RBV must always be taken with food.

In Part A and Part B:

If a subject misses a dose of MK-5172 and/or MK-8742 and it is less than 8 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. Subject should not double the next dose in order to compensate for what has been missed.

If a subject misses a dose of RBV, then they should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then these missed doses should be skipped, and the normal dosing schedule should be resumed. Subjects should not double the next dose in order to "make up" what has been missed.

5.2.3 Trial Blinding/Masking

In Part A:

In the RBV containing arms, a double-blind/masking technique will be used: MK-8742 and placebo to MK-8742 will be packaged identically so that treatment blind/masking is maintained. The subject, the investigator, and study site personnel who are involved in the treatment or clinical evaluation of the subjects will be blinded to the treatment group assignments. The sponsor will not be blinded to the treatment group assignments. The RBV free arm will not be blinded to dose of MK-8742.

In Part B:

Part B is an open-label trial; therefore, the Sponsor, investigator, and subject will know the dose of the therapy administered. However, the investigator and subject will be blinded to the duration of therapy from randomization through Week 8 or Week 12 (except for Arm 12 and Arm 13), depending on their treatment arm. The sponsor will remain unblinded to dose and duration throughout the study.

See Section 7.2, Assessing and Recording Adverse Events, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

For Part A:

Randomization will occur centrally using an interactive voice response system (IVRS). There are 3 treatment arms. Subjects will be assigned randomized treatment in an 2:2:3 ratio to one of the following treatment arms for GT 1b subjects, and in a 1:1 ratio to the first two treatment arms for GT1a subjects:

- MK-5172 100 mg + MK-8742 20 mg + RBV
- MK-5172 100 mg + MK-8742 50 mg + RBV
- MK-5172 100 mg + MK-8742 50 mg

For Part B:

Randomization will occur centrally using an interactive voice response system (IVRS). In Part B, there are 13 treatment arms. Subjects will be assigned and randomized based on subject population and disease characteristics (cirrhotic or non-cirrhotic).

Treatment Naïve (Non-cirrhotic: Arms 1-3):

GT1a subjects will be randomized to 3 treatment arms in a ratio of 2:1:2 to receive 8 weeks of open label MK-5172 100 mg + MK-8742 50 mg + RBV, or 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV. GT1 non-a subjects will all be allocated to receive 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg + RBV.

Treatment Naïve (Cirrhotic: Arms 4-7)

Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.

Null-responders (Cirrhotic or Non-cirrhotic: Arms 8-11):

Subjects will be randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.

Treatment Naïve with HIV co-infection (Non-cirrhotic: Arms 12-13):

Subjects will be randomized to 2 treatment arms in a ratio of 1:1 to receive 12 weeks of open label MK-5172 100 mg + MK-8742 50 mg, +/- RBV.

5.4 Stratification

Randomization will be stratified according to the following factor:

- In Part A: The IVRS will stratify subjects based on Genotype (1a vs. 1b), and at least 50% of treatment arms 1 and 2 will be comprised of GT 1a subjects
- In Part B: The IVRS will stratify the subjects within each subject population as follows: TN non-cirrhotic subjects based on Genotype (1a vs 1 non-a); TN cirrhotic subjects based on Genotype (1a vs 1 non-a); Null-responders based on Genotype (1a vs 1 non-a) and cirrhosis status (non-cirrhotic vs cirrhotic); TN Co-infected with HIV based on Genotype (1a vs 1 non-a). See Section 2.1, Trial Design, for specific information regarding stratification by GT and subject population.

5.5 Concomitant Medications (allowed & prohibited)

Drugs specifically prohibited in the exclusion criteria are not allowed during the dosing period. Listed below are some specific restrictions for concomitant therapy use during the dosing period. If there is a clinical indication for one of these or other medications specifically prohibited during dosing period, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator, the Sponsor and the subject.

Part A and Part B:

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

Strong CYP3A/P-gp inhibitors, including but not limited to:

- Antibiotics: clarithromycin, erythromycin, telithromycin
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antihypertensives: nifedipine
- Nefazodone

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, ritonavir, atazanavir, saquinavir, tipranavir, lopinavir
- Diabetes agents: glibenclamide, glyburide
- Lipid lowering agents: gemfibrozil
- eltrombopag
- lapatinib
- grapefruit/grapefruit juice

HIV medications, including but not limited to:

- efavirenz
- etravirine
- ritonavir
- all HIV protease inhibitors

All HMG-CoA reductase inhibitors (statins)

The following classes of drugs:

- Proton pump inhibitors
- H₂ antagonists
- Other anti-ulcer agents and gastric acid suppressants

In general, CYP3A4 substrates with narrow therapeutic ranges (e.g. warfarin, amiodarone, flecainide, propafenone, quinidine, fentanyl, sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension) 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.

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.

Herbal supplements are prohibited. Only silymarin (Milk Thistle, *Silybum marianum*) is permitted during the trial

Medications contraindicated during therapy with RBV are not permitted in this trial.

5.6 Rescue Medications & Supportive Care

Rescue therapy for individual subjects who meet virologic failure criteria (futility, rebound, breakthrough, relapse) or discontinue due to safety:

In Part A:

Optional rescue therapy will be offered to any subject who meets the criteria for virologic failure or discontinues study medications due to safety concerns that are not attributed to RBV. Subjects must start on rescue within 4 months from the time of discontinuing therapy or within 4 months of follow-up week 24 in case of relapse. The Sponsor will provide rescue medications through local sourcing or a central distribution site, depending on country requirements; however, subjects who receive this rescue therapy will not be followed and no data will be collected during rescue in this trial.

Rescue regimen for individual subjects will consist of Peg-IFN alfa-2b (1.5 µg/kg/wk) + RBV (weight-based) and will be administered as per the product label for 48 weeks. Subjects must have no contraindications to Peg-IFN-alfa-2b.

Since the rescue therapy includes Peg-IFN alfa-2b, subjects with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams as indicated, and any subject who develops ocular symptoms should receive a prompt and complete eye examination as specified in the Peg-IFN alfa-2b product label.

In Part B:

Rescue therapy will not be offered in Part B. Please see Section 4.2.2 for Rationale.

Treatment arm modification:

In Part A:

For treatment arms with an unacceptable rate of relapse (>3 subjects in the per-protocol population in arms 1 and 2, or >2 subjects in the per-protocol population in arm 3), at the point when the relapse rate is identified, all remaining subjects still on treatment, regardless of where they are in the 12 week regimen will have Peg-IFN alfa-2b added (and RBV added in arm 3) through the remaining 12 weeks of therapy. In addition, their treatment will be

extended to include an additional 12 weeks of Peg-IFN alfa-2b + RBV. In this case of treatment arm modification, Peg-IFN alfa-2b (and RBV for arm 3) will be dispensed via IVRS. Dosing will be immediately halted for subjects who decline treatment arm modification.

In Part B:

For arms with an unacceptable rate of relapse (>5 subjects in the per-protocol population in any treatment arm), at the point when the relapse rate is identified, all remaining subjects still on treatment, regardless of where they are in their regimen will have Peg-IFN alfa-2b added (and RBV added in the RBV free arms) through the remaining weeks of therapy. In addition, their treatment will be extended to include an additional 12 weeks of Peg-IFN alfa-2b + RBV. In this case of treatment arm modification, Peg-IFN alfa-2b and RBV will be dispensed via IVRS. Dosing will be immediately halted for subjects who decline treatment arm modification.

5.7 Diet/Activity/Other Considerations

Diet Considerations

In Part A:

MK-5172, MK-8742/placebo, and RBV (in the RBV containing arms) should be taken together once daily. MK-5172 and MK-8742 do not need to be taken with food, however, RBV must be taken with food. A second daily dose of RBV (in the RBV containing arms) should be taken alone, with food.

In Part B:

MK-5172 and MK-8742 can be taken without regard to food. RBV (in the RBV containing arms) must be taken with food. When MK-5172 and MK-8742 are taken without RBV, they can be taken without regard to food. When MK-5172 and MK-8742 are taken with RBV, they must be taken with food. Intake of grapefruit or grapefruit juice is contraindicated during the treatment period of the trial.

Considerations for Screening Visit

In Part A:

Fasting glucose will be tested only at the Screening. Subjects must fast from all food and drink (except for water) a minimum of 8 hours prior to blood sample collection.

In Part B:

Fasting glucose will not be tested in Part B.

Considerations for Study Visits (Part A and Part B)

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 13](#) and [Table 14](#) in Section 7.1.4.2.1.

5.8 Subject Withdrawal/Discontinuation Criteria (Part A and Part B)

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. Discontinuation from treatment is permanent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin treatment again.

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

1. The subject or legal representative (such as a parent or legal guardian) withdraws consent.
 - Request of the subject (subjects have the right to discontinue treatment at any time for any reason).

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 virologic failure criteria (see section 4.2.3.1.1.2)
- Subject becomes pregnant during the trial.
- A physician investigator feels it is in 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 >1.5.
- 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 >1.5.

- The subject's ALT or AST increases to $>3\times$ 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 and or MK-8742: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia ($>5\%$).
- The subject's ALT or AST increases to $>3\times$ 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 and or MK-8742: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia ($>5\%$).
- The subject's alkaline phosphatase increases to $>3\times$ ULN, there is a simultaneous increase in total bilirubin $> 2\times$ ULN and other causes of elevated alkaline phosphatase are excluded.
- The subject's alkaline phosphatase increases to $>5\times$ ULN and other causes of elevated alkaline phosphatase are excluded.
- The subject experiences HIV-1 virologic failure (for subjects enrolled in HIV co-infected arm only). HIV-1 virologic failure is defined as HIV-1 RNA 200 copies/mL confirmed on two consecutive tests at least 2 weeks apart, in subjects compliant with their HIV ARV therapies.
- A subject may be discontinued from treatment for any of the following reasons:
 1. 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.
 2. Failure to comply with the dosing, evaluations, or other requirements of the trial

5.9 Subject Replacement Strategy (Part A and Part B)

A subject that 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 trial 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

Early Trial Termination Due to Safety Criteria:

In Part A: If >3 of 24 subjects in any single arm meet any of the safety criteria listed below, that particular study arm will be discontinued and all other study arms will be reviewed to determine if any additional arms should be terminated. **For Part B:** Similar action as in Part A will be taken if >5 of 30 in a particular arm meet any of the following:

- ALT or AST increases to >500 IU/L.
- 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 >1.5.
- 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 >1.5.
- 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%).
- 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%).
- alkaline phosphatase increases to >3x ULN, a simultaneous increase in total bilirubin > 2x ULN and other causes of elevated alkaline phosphatase are excluded.
- alkaline phosphatase increases to >5x ULN and other causes of elevated alkaline phosphatase are excluded.

Early Trial Termination Due to Failure Criteria (futility, rebound, breakthrough, relapse):

For Part A: If >3 subjects in the per-protocol population of study arms 1 and 2, or >2 subjects in the per-protocol population in study arm 3 meet a failure criteria (i.e. futility, rebound, breakthrough, relapse), that particular study arm will be discontinued and all other study arms will be reviewed to determine if any additional study arms should be terminated.

For Part B, all Early Trial Termination decisions will be based on the per-protocol population.

HCV failure criteria In Part B:

For Study Arms 1-3 and 12-13:

If 3 out of the first 12 subjects fail, or, if a total of 5 subjects in a single arm fail, then enrollment into that arm will halt and all other arms will be reviewed to determine if any additional arms should be terminated.

For Study Arms 4-11:

If 3 out of the first 12 subjects fail, or if a total of 6 subjects in a single arm fail, then enrollment into that arm will halt and all other arms will be reviewed to determine if any additional arms should be terminated.

HIV failure criteria In Part B:

If >2 subjects enrolled into either arm 12 or arm 13 experience confirmed loss of HIV virologic suppression, that particular arm will halt enrollment of additional subjects and the other co-infected arm will be reviewed to determine if it should also be terminated.

Viral failure is defined as HIV RNA ≥ 200 copies/mL confirmed on two consecutive tests at least 2 weeks apart, in subjects compliant with their HIV ARV therapies.).

Treatment arm modification of study arms:

For Part A: If an unacceptable rate of relapse (>3 subjects in the per-protocol population in RBV containing arms 1 and 2, or >2 subjects in the per-protocol population of arm 3) is encountered in any arm, additional enrollment into that study arm will be halted and all other arms would be evaluated for modification. The subjects still on therapy in that arm will be recommended for treatment arm modification (see Section 5.6).

For Part B: If an unacceptable rate of relapse (>5 subjects in the per-protocol population in any arm) is encountered, additional enrollment into that study arm will be halted and all other arms would be evaluated for modification. The subjects still on therapy in that arm will be recommended for treatment arm modification (see Section 5.6).

6.0 TRIAL FLOW CHART

For Part A:

Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Study Period ¹	Treatment Week 1					Treatment Weeks														Follow-Up Weeks				
	Scr	Day 1	Day 3	Day 5	Day 7	2	3	4	5	6	7	8	9	10	11	12	Viral Fail Conf Visit	Unsched/ Early Discon Visit	FU 2	FU 4	FU 8	FU 12	FU 24	
STUDY PROCEDURESs																								
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	x	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	x	x	x	x	x	x	x	x						
CLINICAL SAFETY EVALUATIONS																								
Physical Examination	x	x				x		x				x				x		x		x		x	x	
Weight	x	x														x							x	
Height	x																							
12-Lead ECG ²	x															x		x					x	
Vital Signs ³	x	x						x				x				x	x	x	x	x	x	x	x	
Subject confirmation of birth control ⁴	x	x						x				x				x	x	x	x	x	x	x	x	
Review (Serious) Adverse Events ⁵	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
LABORATORY SAFETY EVALUATIONS ⁶																								
Antinuclear antibody (ANA)	x																							
Coagulation	x	x	x	x	x	x	x	x	x	x	x	x	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	x	x	x	x	x	x	x	x	x	
HBA1C (only for subjects with diabetes or glucose above lab reference ranges)	x																							

Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Study Period ¹		Treatment Week 1				Treatment Weeks														Follow-Up Weeks				
	Scr	Day 1	Day 3	Day 5	Day 7	2	3	4	5	6	7	8	9	10	11	12	Viral Fail Conf Visit	Unsched/ Early Discon Visit	FU 2	FU 4	FU 8	FU 12	FU 24	
STUDY PROCEDURESs																								
Fasting Plasma Glucose	x																							
Thyroid Stimulating Hormone (TSH) level	x	x														x						x		
Urinalysis	x															x							x	
Urine Pregnancy Test (females of child bearing potential only) ⁷	x	x						x				x				x	x	x	x	x	x	x	x	
PHARMACOKINETICS⁸																								
MK-5172 PK		x	x	x	x	x	x	x		x		x		x		x	x	x						
MK-8742 PK		x	x	x	x	x	x	x		x		x		x		x	x	x						
RBV PK		x	x	x	x		x	x								x	x	x						
HCV EVALUATIONS																								
HCV Genotype Determination	x																							
HCV RNA Level ⁹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X ¹⁹	x	x	x	x	x	
Plasma and serum for Viral Resistance and Biomarker ¹⁰		x	x	x	x	x		x		x		x		x		x	x	X ¹⁹	x	x	x	x	x	
RNA Profile Sample ¹¹		x	x	x	x			x								x		x						
DNA for <i>IL28B</i> Genotyping and genetic analysis ¹²		x																						
Plasma for Future Biomedical Research ¹³		x																						
DNA for Future Biomedical Research		x																						
DRUG ADMINISTRATION																								
MK-5172 ¹⁵		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ¹⁸								
MK-8742/Placebo ¹⁶		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ¹⁸								
RBV (open-label) ¹⁷		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ¹⁸								
Peg-IFN (open-label) ²⁰		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ¹⁸								

- ¹ Visits should be scheduled as close to the indicated study period as possible.
- ² All 12-Lead ECGs will be obtained after the subject has remained in a semi-recumbent position for 10 minutes.
- ³ 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 measurement of vital signs.
- ⁴ Subject and subject's partner(s) must each use acceptable methods of contraception from 2 weeks prior to treatment and for at least 6 months after the last dose of study drug or longer, if dictated by local regulation.
- ⁵ 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.
- ⁶ Refer to [Table 12](#) in Section 7.1.4.1, Laboratory Procedures/Assessments, for further details regarding the laboratory safety tests.
- ⁷ 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.
- ⁸ Blood samples will be collected from all subjects. Refer to [Table 13](#) for further details regarding the collection time points.
- ⁹ Blood samples will be collected for HCV RNA levels. Samples may be taken irrespective of the dose time unless required by PK sample collection.
- ¹⁰ Blood samples will be collected for viral resistance testing, proteomics, and metabolomics and other exploratory analysis. Serum will be collected only at Day 1, Weeks 4, 8, and 12.
- ¹¹ Blood samples will be collected for RNA profiling. Leftover RNA samples will be stored for Future Biomedical Research if the subject signs the Future Biomedical Research consent form.
- ¹² Blood sample will be collected for *IL28B* genotyping and genetic analysis for ADME and HLA genes. The sample will be split into 2 aliquots for each analysis.
- ¹³ Informed Consent for future biomedical research samples must be obtained before the DNA and plasma samples are collected. DNA for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. Plasma samples for FBR must be obtained on Day 1, after consent is obtained.
- ¹⁴ Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.
- ¹⁵ MK-5172 will be provided on a monthly basis. The site will call the Interactive Voice Response System (IVRS) to obtain component ID assignment.
- ¹⁶ MK-8742/Placebo will be provided on a monthly basis. The site will call the Interactive Voice Response System (IVRS) to obtain component ID assignment.
- ¹⁷ For the RBV containing arms, RBV will be provided on a monthly basis. The site will call the Interactive Voice Response System (IVRS) to obtain component ID assignment.
- ¹⁸ Study drug is not dispensed at this visit.
- ¹⁹ If a subject is confirmed 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.
- ²⁰ Should treatment arm modification be recommended (see section 5.6), the Peg-IFN will be added at next available study visit after notification to site. This may occur at any time during the 12 weeks of therapy. N/A for Part B.

Treatment Arm Modification¹				
Visit No.	25	26	27	28
Study Period ²	Treatment Weeks			
	14	16	20	24
STUDY PROCEDURES				
ADMINISTRATIVE PROCEDURES				
Prior and Con-med Review	x	x	x	x
Review Study Medication Diary	x	x	x	x
CLINICAL SAFETY EVALUATIONS				
Physical Examination	x	x	x	x
Vital Signs ³	x	x	x	x
Subject confirmation of birth control ⁴	x	x	x	x
Review (Serious) Adverse Events ⁵	x	x	x	x
LABORATORY SAFETY EVALUATIONS⁶				
Coagulation	x	x	x	x
Chemistry & Hematology	x	x	x	x
Thyroid Stimulating Hormone (TSH) level	x	x	x	x
Urinalysis	x	x	x	x
Urine Pregnancy Test (females of child bearing potential only) ⁷	x	x	x	x
HCV Evaluations				
HCV RNA Level	x	x	x	x
Plasma and serum for Viral Resistance and Biomarker ⁸	x	x	x	x
RNA Profile Sample ⁹	x	x	x	x
DRUG ADMINISTRATION				
RBV (open-label)	x	x	x	x
Peg-IFN (open label)	x	x	x	x

- ¹ Should treatment arm modification be recommended (see section 5.6), subjects in the affected treatment arm would receive 12 additional weeks of Peg-IFN/RBV therapy. At the completion of these extra visits the subjects will follow the main study flowchart with regard to the Follow-up visits 2, 4, 8, 12 and 24 weeks after the end of rescue therapy. Should the subject be discontinued early from treatment in this relapse rescue regimen, the subjects should follow the Early discon/unscheduled or failure confirmation visits defined in the main study flow chart. N/A for Part B.
- ² Visits should be scheduled as close to the indicated study period as possible.
- ³ 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 measurement of vital signs.
- ⁴ Subject and subject's partner(s) must each use acceptable methods of contraception from 2 weeks prior to treatment and for at least 6 months after the last dose of study drug or longer, if dictated by local regulation.
- ⁵ 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.
- ⁶ Refer to [Table 12](#) in Section 7.1.4.1, Laboratory Procedures/Assessments, for further details regarding the laboratory safety tests.
- ⁷ 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.
- ⁸ Blood samples will be collected for viral resistance testing, proteomics, and metabolomics and other exploratory analysis. Blood samples will be collected for RNA profiling. Leftover RNA samples will be stored for Future Biomedical Research if the subject signs the Future Biomedical Research consent form.

Study Flow Chart Part B:

8 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1 ²³	Day 7	2	4	8	NA	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
12 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
18 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	16	18	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Treatment Arm Modification	NA	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		NA	NA	NA	NA	NA	12	16	18	20	24	28	30	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	145	15	16	17	18
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	x	x					x	x
Treatment Allocation/Randomization		x																	
Review Study Medication Diary		x	x	x	x	x	x	x	x	x	x	x	x					x	x
CLINICAL SAFETY EVALUATIONS																			
Physical Examination ¹	x	x			x									x					x
Weight	x	x												x					x
Height	x																		
12-Lead ECG	x				x		X ²²							x					x
Vital Signs	x	x	x	x	x	x	x	x	x					x				x	x
Subject confirmation of birth control	x	x			x	x	x	x	x	x	x	x	x	x	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	x	x	x	x
PATIENT REPORTED OUTCOME																			
SF-36v2® Health Survey		x			x	x ³	x ³		x ³							x	x		x

8 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1 ²³	Day 7	2	4	8	NA	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
12 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
18 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	16	18	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Treatment Arm Modification	NA	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		NA	NA	NA	NA	NA	12	16	18	20	24	28	30	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	145	15	16	17	18
LABORATORY SAFETY EVALUATIONS																			
Coagulation	x	x	x	x	x	x	x	x	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	x	x	x	x	x
HBA1C (only for subjects with a prior diagnosis of diabetes)	x																		
HBsAg	x																		
HIV RNA ²⁴	x																		
AFP	x																		
Urine Pregnancy Test (females of child bearing potential only) ⁴	x	x			x	x	x	x	x	x	x	x		x	x	x	x	x	x
PHARMACOKINETICS																			
MK-5172 PK		x	x	x	x	x	x ²¹	x ²²	x ²²									x	x
MK-8742 PK		x	x	x	x	x	x ²¹	x ²²	x ²²									x	x
RBV PK		x	x		x	x	x ²¹		x ²²									x	x
HCV EVALUATIONS																			
HCV Genotype Determination	x																		
HCV RNA Level	x	x	x	x	x ²⁵	x	x	x	x	x	x	x	x	x	x	x	x	x	x ¹⁴
Plasma for HCV Viral Resistance and Biomarker ⁵		x												x	x	x	x	x	x ¹⁴
Blood (DNA) for IL28B Genotyping and genetic analysis ⁵		x																	
Blood for RNA Profiling ⁷		x	x			x								x					
Blood (DNA) for Future Biomedical Research ⁸		x																	

8 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1 ²³	Day 7	2	4	8	NA	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
12 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	NA	NA	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
18 Week Treatment Regimen	Scr	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		Day 1	Day 7	2	4	8	12	16	18	NA	NA	NA	NA	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Treatment Arm Modification	NA	Treatment Weeks												Follow-Up Weeks				Unscheduled Visits	
		NA	NA	NA	NA	NA	12	16	18	20	24	28	30	FU 4	FU 8	FU 12	FU 24	Unsched/HIV/H CV Viral Fail Conf Visit	Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	145	15	16	17	18
HIV EVALUATIONS ⁹																			
HIV RNA		x			x	x	x							x	x	x	x	x	x
Plasma for HIV Viral Resistance																		x ¹⁰	
CD4+ T-cell counts	x	x			x	x	x							x	x	x	x	x	x
DRUG ADMINISTRATION																			
MK-5172 (open-label) ^{11, 12}		x	x	x	x	x ¹⁵	x ¹⁶	x	x ¹⁷										
MK-8742 (open-label) ¹²		x	x	x	x	x ¹⁵	x ¹⁶	x	x ¹⁷										
RBV (open-label) ¹³		x	x	x	x	x ¹⁵	x ¹⁶	x	x ¹⁷	x	x	x	x						
Peg-IFN (open-label) ¹⁹			x	x	x	x	x	x	x	x	x	x	x ²⁰						

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 PRO SF-36v2® Health Survey will be done only on Day 1, WK4, the end of therapy visit, FU 12, FU 24, and early discontinuation visits for all subjects. For subjects receiving 8, 12, or 18 weeks duration therapy, the end of therapy visits will be week 8, week 12, and week 18, respectively.

⁴ 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 Blood samples will be collected for HCV viral resistance testing at baseline, viral failure confirmation visit, and FU visits. At the same time points, samples will be collected for proteomics, and metabolomics and other exploratory analysis.

⁶ Blood sample will be collected for *IL28B* genotyping and genetic analysis for ADME and HLA genes. The sample should be sent as a single whole blood sample and the testing facility will extract DNA and split into 2 aliquots for each analysis.

⁷ Blood samples will be collected for RNA profiling through the main consent. .

⁸ Informed Consent for future biomedical research samples must be obtained before the DNA samples are collected. DNA for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. Any leftover plasma from HCV RNA, leftover plasma for HCV viral resistance and biomarker, and leftover RNA profile samples will be stored for future research if the subject consents to participate in the FBR sub-study.

⁹ HIV Evaluation is only applicable for HIV co-infected population.

¹⁰ Blood samples will be collected for HIV viral resistance at the time of HIV RNA failure confirmation, the sample will be shipped to the referral laboratory.

¹¹ Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.

¹² MK-5172 and MK-8742 will be provided on a monthly basis. The site will call the Interactive Voice Response System (IVRS) to obtain component ID assignment. Duration will be based on allocation schedule, some treatment arms will be either 8, 12, or 18 weeks in duration.

¹³ RBV will be provided on a monthly basis. The site will call the Interactive Voice Response System (IVRS) to obtain component ID assignment. Duration or inclusion will be based on allocation schedule, some treatment groups will be RBV-free

¹⁴ If a subject is confirmed 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.

¹⁵ There will be no dispensing of study medication on this day for subjects receiving 8 weeks of therapy. However, the subject will take their last dose(s) of week 8 on that day.

¹⁶ 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.

¹⁷ There will be no dispensing of study medication on this day for subjects receiving 18 weeks of therapy. However, the subject will take their last dose(s) of week 18 on that day.

¹⁸ Should treatment arm modification be recommended (see Section 5.6), subjects in the affected treatment arm would receive 12 additional weeks of Peg-IFN/RBV therapy. At the completion of these extra visits, the subjects will complete the FU visits as outlined in this flowchart.

¹⁹ Peg-INF only to be administered in the case of treatment arm modification.

²⁰ There will be no dispensing of study medication on this day for subjects receiving treatment arm modification.

²¹ Only applicable for subjects receiving 12 or 18 weeks of therapy.

²² Only applicable for subjects receiving 18 weeks of therapy.

²³ Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.

²⁴ HIV RNA is collected for all subjects at Visit 1 (screening) to determine if HIV +.

²⁵ If HCV RNA at TW 4 is ≥ 25 IU/mL, the subject should return for an unscheduled visit (Visit 17) in 2 weeks to confirm that the subject has not experienced rebound or virologic breakthrough.

7.0 TRIAL PROCEDURES

This Section pertains to both Part A and B unless otherwise noted.

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 must obtain documented consent from each potential subject 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 after the subject provides written informed consent.

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 treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated to trial treatment and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. 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 a Study Medication Diary to be completed during the study period. The investigator/study coordinator will be responsible for entering the subject's identification (allocation number), visit number, and dates before giving the diary card 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 diary card for the entire time period. Only the subject should enter information on the diary card. The subject is to return the completed diary card at each scheduled visit. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the dosing diary 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 diary card. The subject will initial the diary card to confirm that the information is accurate. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

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

A complete physical examination, performed at the Screening visit 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.

7.1.2.2 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.

7.1.2.3 12-Lead ECG

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

7.1.2.4 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.

7.1.2.5 Birth Control Confirmation

Extreme care must be taken to avoid pregnancy in female subjects of childbearing potential and female partners of childbearing potential of male subjects.

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.

7.1.2.6 Adverse Events

During the screening period only SAEs should be recorded.

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

7.1.2.7 Complete Ocular Examination (for Peg-IFN alfa-2b based Treatment Arm Modification eligibility)

An ocular exam should be conducted on all subjects who are placed on Peg-IFN as part of Treatment Arm Modification as per the Peg-IFN alfa-2b label.

7.1.3 Patient-Reported Outcomes (Part B Only)

SF36v2® Health Survey

Health-related quality of life will be assessed using the SF-36v2® Health Survey, Acute (1-week recall) Form, a generic health survey, which includes 36 questions to measure functional health and well-being from the patient's perspective. The SF-36 has been used in several HCV-positive populations and clinical trials for the treatment of HCV infection [46,47]. 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.

Subjects are to complete the SF-36v2® on their own during the appropriate study visit (see study flow chart for Part B: Day 1, Week 4 Visit, End of Therapy Visit (which may be Week 8, 12 or Week 18 Visit) or Early Discontinuation Visit, Follow-up Week 12, and Follow-up Week 24) prior to being seen by the investigator, receiving study treatment, discussing any medical conditions, or receiving any medical results. It should take subjects approximately 5-10 minutes to complete the SF-36v2®.

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 12.5.

7.1.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in [Table 12](#).

Table 12 Laboratory Tests

Hematology	Chemistry	Urinalysis (Part A only)	Other
Hematocrit	Albumin	Specific Gravity	Hemoglobin A1C (HbA1c)
Hemoglobin	Alkaline phosphatase	pH	Hepatitis C Virus Genotype
Platelet count	Alanine aminotransferase (ALT)	Glucose	Prothrombin time (PT)
WBC (total and differential)	Aspartate aminotransferase (AST)	Protein	Activated partial thromboplastin time (aPTT) (Part A only)
Erythrocytes (RBC count)	Creatinine	Ketones	International normalized Ratio (INR)
	Creatinine Clearance (screening only)	Occult Blood	Choriogonadotropin Beta (Urine pregnancy test kits to sites)
	Creatine Kinase	Bilirubin	CD4 + T-cell count (Part B only)
	Gamma-glutamyltransferase	Nitrite	Plasma HIV-1 RNA (Part B only)
	Glucose (serum glucose)	Leukocytes	Plasma HCV RNA
	Potassium	Erythrocytes	HBsAg (Part B only)
	Sodium	Microscopic exam, if abnormal results are noted	
	Total Bilirubin		APRI calculation (Part B only)
	Direct Bilirubin		Fibrosure® (Fibrotest) as requested by site for entry criteria (may be performed locally)
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Thyrotropin (TSH) (Part A, and prior to treatment arm modification Part B only)		
	Free triiodothyronine (free T3) (Part A and prior to treatment arm modification Part B only); this test will be run if TSH result is > ULN or <LLN.		
	Thyroxine Free (free T4) (Part A and prior to treatment arm modification Part B only); this test will be run if TSH result is > ULN or <LLN.		
	Fasting plasma glucose (screening only) (Part A only)		
	AFP		
	Amylase		
	Lipase		
	ANA (Part A and in Part B prior to treatment arm modification)		

7.1.4.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Departments of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and the appropriate department within Early-Stage Development. 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 Pharmacokinetic Sampling

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

Population PK samples will be collected from all subjects in this study (i.e. sparse PK sampling scheme) as outlined in [Table 13](#) (for Part A) and [Table 14](#) (for Part B). Not all PK samples from each visit will be analyzed; specific timepoints may be analyzed for individual subjects to verify compliance with study medications in the event of virological failure or to evaluate the relationship between an adverse event and PK parameters. On all PK visits, except Visits 6, 10, 17, and 18, subjects 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.

Table 13 Pharmacokinetic Sampling Timepoints (Part A)

Visit Number	Study Day/Week	Time Relative to Dose of MK-5172, MK-8742, and RBV ⁴	MK-5172 PK Sample ¹	MK-8742 PK Sample ¹	RBV PK Sample ²
2	Day 1	Predose	x	x	x
3	Day 3	Predose	x	x	x
4	Day 5	Predose	x	x	x
5	Day 7	Predose	x	x	x
6	Week 2	6-20 hrs post-dose	x	x	
7	Week 3	Predose	x	x	x
8	Week 4	Predose	x	x	x
		~2 hrs Postdose	x	x	
		~4 hrs Postdose	x	x	
10	Week 6	6-20 hrs post-dose	x	x	
12	Week 8	Predose	x	x	
14	Week 10	Predose	x	x	
16	Week 12	Predose	x	x	x
		~2 hrs Postdose	x	x	
		~4 hrs Postdose	x	x	
17	Viral Failure Conf Visit	NA ³	x	x	x
18	Unsched/Early Discon Visit	NA ³	x	x	x
¹ ~4 mL of blood will be collected at each specified time point for plasma PK assessments of MK-5172 and MK-8742. ² ~3 mL of blood will be collected at each specified time point for plasma PK assessment of RBV for subjects in the RBV containing arms. ³ Time Relative to last Dose of MK-5172, MK-8742, and RBV must be recorded in INFORM ⁴ The date and time of the last MK-5172, MK-8742, and RBV dose prior to all PK sample collection 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-5172, MK-8742, and RBV dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary).					

Table 14 Pharmacokinetic Sampling Timepoints (Part B)

Visit Number	Study Day/Week	Time Relative to Dose of MK-5172, MK-8742, and RBV ⁴	MK-5172 PK Sample ¹	MK-8742 PK Sample ¹	RBV PK Sample ²
2	Day 1	Predose	x	x	x
3	Day 7	Predose	x	x	x
4	Week 2	6-20 hrs post-dose	x	x	
5	Week 4	Predose	x	x	x
		~2 hrs Postdose	x	x	
		~4 hrs Postdose	x	x	
6	Week 8	Predose	x	x	x
7 ⁵	Week 12	Predose	x	x	x
		~2 hrs Postdose	x	x	
		~4 hrs Postdose	x	x	
8 ⁶	Week 16	Predose	x	x	
9 ⁶	Week 18	Predose	x	x	x
17	Unsched/Viral Failure Conf Visit	NA ³	x	x	x
18	Early Discon Visit	NA ³	x	x	x

¹ ~4 mL of blood will be collected at each specified time point for plasma PK assessments of MK-5172 and MK-8742.
² ~3 mL of blood will be collected at each specified time point for plasma PK assessment of RBV for subjects in the RBV containing arms.
³ Time Relative to last Dose of MK-5172, MK-8742, and RBV must be recorded in INFORM
⁴ The date and time of the last MK-5172, MK-8742, and RBV dose prior to all PK sample collection must be recorded in INFORM
⁵ Only applicable for subjects receiving 12 or 18 weeks of therapy
⁶ Only applicable for subjects receiving 18 weeks of therapy
Note: At the time of PK sample collection, subjects will be asked to provide information regarding, the time/date of the last MK-5172, MK-8742, and RBV 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:

- Blood (DNA) for Future Biomedical Research (for Part A and Part B)
- Plasma for Future Biomedical Research (for Part A)
- Leftover main study RNA samples (for Part A and Part B)
- Leftover main study plasma samples (from HCV RNA, viral resistance and biomarkers) (for Part B)

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

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 as part of the main consent for inclusion in the study.
- Blood must be drawn from each subject as part of the main consent to assess HCV RNA plasma levels at various time points as shown in the flow chart. HCV-RNA in plasma will be measured using a COBAS™ Taqman™ HCV Test, v2.0 ® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. In Part B, any 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 as part of the main consent to assess viral resistance mutation and processed as instructed by the central laboratory manual.
- Protein, RNA levels , including mRNA profiling, 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 *IL28B* genotyping and genetic analysis for ADME and HLA genes associated with liver injury are obtained at Day 1 as part of the main consent. The assay performed is specific to the *IL28B* gene region and genes related to HLA and ADME. Any remaining specimen after the genetic analysis has been performed will be destroyed.
- A sample for RNA Profile is collected from all subjects on different timepoints as part of the main consent. Any leftover samples may be used for additional exploratory analyses only if the subject signed for future biomedical consent. Otherwise the left over sample will be discarded at the end of the study.

7.1.4.5 HIV Evaluation (Part B only)

The following specimens are to be obtained as part of efficacy measurements:

- Blood must be drawn from each subject as part of the main consent to assess HIV RNA plasma levels at various time points as shown in the flow chart for Part B (Section 6). HIV-RNA in plasma will be measured using a Roche Cobas Ampliprep/Taqman v 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) as part of the main consent to assess viral resistance mutation, and processed as instructed by the central laboratory manual. HIV-1 drug

resistance will be assessed using the PhenoSense™ HIV Assay, GeneSeq™ HIV Assay, and the PhenoSense Integrase Assay GeneSeq Integrase assay.

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

7.1.5 Other Procedures

7.1.5.1 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:

- Antinuclear antibody (ANA) (Part A only)
- HCV GT Determination
- Liver biopsy
- 12-Lead ECG

Part A:

Subjects may be retested once within the 45-day screening window if their laboratory results are outside the specified criteria. If a single value is within 10% of the listed laboratory value, and the value is considered not to be clinically significant by the investigator, the subject may be considered for enrollment.

If a subject is excluded due to the platelet criteria not being met ($<150 \times 10^3/\mu\text{L}$); no retests can be performed and ranges (for e.g. within 10% of exclusion criterion value) cannot be utilized

Part B:

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

7.1.5.2 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 13](#) and [Table 14](#) in Section 7.1.4.2.1.

7.1.5.3 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, 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.

7.1.5.3.1 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 writing to 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.

7.1.5.4 Blinding/Unblinding

For Part A, IVRS/IWRS should be used for emergency unblinding treatment assignment in the event that this is required for subject safety.

Part B of this study is an open label trial however, subjects will be blinded to duration of therapy. For Part A, IVRS/IWRS

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 (Visit 1)

Within 45 days prior to administration of the initial dose of study drug, potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Sections 5.1. Verification should be obtained to confirm that the subject either

cirrhotic or non-cirrhotic (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.

Subjects will be instructed that they are required to use two acceptable methods of birth control from at least 2 weeks prior to Day 1, throughout treatment, and for at least 6 months (or longer if dictated by local regulations) after the last dose of study medication.

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 Study/Treatment Visits

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. Subjects should be fasting for 8 hours prior to sample collection (Part A only). 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, 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 and host RNA profiling related to the response of HCV subjects to MK-5172, MK-8742, and RBV therapies.

For HIV co-infected subjects in Part B, additional blood samples will be collected for HIV RNA and CD4+ cell counts.

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.

For subjects in Part A, rescue therapy, open label RBV and Peg-IFN alfa-2b can be sourced locally or through the central distribution site, if needed. Rescue therapy is not being offered in Part B.

For subjects who are in a study arm that undergoes treatment arm modification, Peg-IFN+/- RBV will be dispensed via IVRS.

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:

1. The reason the subject discontinued.
2. The date of the last dose of study medications from the trial.
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate.
4. (Serious) Adverse events.
5. Final Assessments: Every effort should be made to ensure that all procedures and evaluations scheduled for the Early Discon Visit are performed.
6. Retrieve all study medications from the subject.

7.1.6.4 Follow-Up Visits

In Part A:

At the completion of study therapy (12 weeks or 24 weeks for subjects receiving treatment arm modification (see Section 5.6)) subjects will return to the study site for follow-up visits at 2, 4, 8, 12, and 24 weeks, after the last dose of study drug. If a subject completes 12 weeks of therapy, the 2, 4, 8, 12, and 24 –week follow-up visits will occur approximately 14, 16, 20, 24, and 36 weeks after Day 1, respectively. If a subject receives the treatment arm modification, follow-up visits will occur approximately 26, 28, 32, 36 and 48 weeks after Day 1, respectively.

Subjects who discontinue because they have met criteria for 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 2, 4, 8, 12, and 24 weeks following the confirmation of virologic failure. Subjects who meet the virologic failure criterion of relapse (having HCV RNA ≥ 25 IU/mL 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 2, 4, 8, 12, and 24 weeks as outlined in the Study Flow Chart (Section 6).

Subjects who discontinue for reasons other than 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 2, 4, 8, 12, and 24 weeks following the discontinuation of treatment.

For Part B:

At the completion of study therapy (8, 12 or 24 weeks) subjects will return to the study sites for follow-up visits at 4, 8, 12, and 24 weeks after the last dose of study drug.

Subjects who discontinue because they have met criteria for virologic failure while on study therapy should complete an Early Discontinuation Visit as outlined in the Study Flow Chart for Part B (Section 6), and return to the study site for follow-up visits at 4, 8, 12, and 24 weeks following the confirmation of virologic failure. Subjects who meet the virologic failure criterion of relapse (having HCV RNA ≥ 25 IU/mL 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 for Part B (Section 6).

Subjects who discontinue for reasons other than virologic failure should complete an Early Discontinuation Visit as outlined in the Study Flow Chart for Part B 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.

7.1.7 Evaluations of Laboratory Safety Signals

Laboratory safety measurements will be evaluated throughout the study as outlined in the Study Flow Chart (in Part A weekly during the first 12 weeks of therapy, followed by bi-weekly visits up to 24 weeks of therapy and in Part B, weekly during the first 2 weeks followed by monthly visits for the rest of the treatment period) 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 (Part A: Wk 12 or Wk 24 for treatment arm modification, Part B: Wk 8, 12, or 18 in the main part of the study or Wk 20, Wk 24, or Wk 30 for treatment arm modification), then the subject should return to the site weekly for additional monitoring until the values normalize.

7.1.8 Trial Unblinding

Treatment group assignment can be shared with sites when all subjects have reached SVR₄ and database is ready for SVR₄ analysis. This procedure will **only** be performed by Sponsor. Routine individual unblinding will not be performed by study personal. For emergency unblinding please refer to Section 7.1.5.4.

Trial Unblinding is not applicable for Part B.

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.

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:

MK-5172: Any intake in excess of the prescribed dose per calendar day

MK-8742: Any intake in excess of the prescribed dose per calendar day

REBETOL™: A dose that exceeds 1600 mg in a 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.

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 14 days of completing the trial. All subjects and female partners of male 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.

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 15](#) 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.

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

When a subject is on study medication, 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.

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
3. first instance of ALT or AST >3x baseline AND >100 IU/L
4. first instance of alkaline phosphatase >3x ULN
5. HIV RNA 200 copies/mL (Arms 12 and 13 only)

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 15](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 15](#) for instructions in evaluating adverse events.

Table 15 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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	<p>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.)</p>
	Rechallenge	<p>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 U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.</p>
	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 Events

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

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Data Analysis Section (DAS) of the protocol details (Section 8.2).

8.1.1 Efficacy Analyses

For Parts A and B, the primary and key secondary efficacy endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in [Table 16](#).

The primary efficacy objective of this study is to estimate the SVR₁₂ rates of each of the treatment arms. A two-sided 95% confidence interval will be constructed for SVR₁₂ for each arm separately. There will be no formal efficacy hypothesis testing conducted in this study.

The key secondary objective will be evaluated using summary statistics to characterize the time to first achievement of undetectable HCV RNA in each treatment arm. The relationship between this endpoint and achievement of SVR₁₂ will also be assessed.

Table 16 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach [†]
Primary:			
Proportion of subjects achieving SVR ₁₂ in each treatment arm	95% confidence interval	Per Protocol	OF
Secondary:			
Time to first achievement of undetectable (TND) HCV RNA in each treatment arm	Kaplan-Meier plot and summary statistics	Per Protocol	DAO
[†] OF = Observed Failure. DAO = Data as observed. Additional details provided in Section 8.2			

8.1.2 Safety Analyses

For Parts A and B, the All-Subjects-as-Treated population will be employed for safety analyses. For this protocol, the proportion of subjects who experience the following adverse events during the study treatment period will be estimated for each arm: gastrointestinal adverse events (vomiting, nausea, and diarrhea) and adverse events of elevated laboratory values that are reported as ECIs during the study therapy period. For Part B, a confirmed detected HIV RNA (viral breakthrough) reported as an ECI would also be included in this analysis.

8.1.3 Power and Sample Size

Part A of this estimation study will randomize approximately 24 subjects in each of the treatment arms that include RBV, and 12 subjects in the treatment arm without RBV. Assuming a protocol violation rate of 10%, the per protocol (PP) population will include approximately 22 subjects per arm with RBV and 11 subjects in the arm without RBV. For the arms with RBV, if the SVR_{12} rate is approximately 82% (18 successes out of 22), the exact 95% CI is (60.8%, 94.4%). If the SVR_{12} rate is approximately 91% (20 successes out of 22), the exact 95% CI is (72.0%, 98.7%). For the arm without RBV, if the SVR_{12} rate is approximately 90% (10 successes out of 11), the exact 95% CI is (58.7%, 99.8%). Detailed information is in 8.2.7.1.

In part B, four subject populations (TN no cirrhosis, TN with cirrhosis, Null-responders no cirrhosis and with cirrhosis, and TN with HIV co-infection no cirrhosis) will be randomized according to the design as illustrated in [Figure 2](#). Approximately 30 subjects from each subject population will be randomized to each treatment arm relevant to that subject population. Precision of the SVR_{12} rate estimates for various possible observed values is shown in 8.2.7.1, assuming an approximate 10% protocol violation rate.

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.

Unless otherwise noted, this section applies to both Parts A and B.

8.2.1 Responsibility for Analyses

The statistical analysis 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.

In Part A, the subjects and study site personnel will be blinded to the MK-8742 dose in the treatment arms with RBV. The Sponsor will not be blinded to treatment arms.

In Part B, the study is open-label but subjects and study site personnel will be blinded to duration until the treatment is completed for a subject. The Sponsor will not be blinded to treatment arms.

8.2.2 Hypotheses/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 will be the proportion of subjects achieving SVR₁₂ in each of the treatment arms.

The secondary efficacy endpoints are:

- 1) the time to first achievement of undetectable (TND) HCV RNA
- 2) the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA < 25 IU/mL at Week 2, Week 4, and Week 12, and end of treatment visits. Note: Week 12 and end of treatment visit may be the same.
- 3) the proportion of subjects achieving SVR₄ and SVR₂₄
- 4) the emergence of antiviral resistance to MK-5172 and MK-8742 when administered as a combination regimen +/- RBV

During the course of the trial, there will be periodic analyses conducted to evaluate safety and efficacy. The purpose of these analyses is for planning the next phase of program development.

These assessments are in addition to the regular medical monitoring that is performed throughout the study.

8.2.3.1.2 Pharmacokinetic Endpoints

Additional details are in 4.2.3.5.

The PK endpoints will be C_{2hr} , C_{4hr} , and C_{trough} .

8.2.3.1.3 Exploratory Endpoints

1. The effect of genetic variation in the human *IL28B* gene as a predictor of virologic response.
2. The effect of biomarkers (proteins, RNA expression, and metabolite production) that may be predictive of the tolerability of study drugs and virologic response to MK-5172 and MK-8742 +/- RBV.
3. The PK of MK-5172, MK-8742, and RBV.
4. The PK/PD relationship which may include MK-5172, MK-8742, and RBV.
5. Change from baseline in health-related quality of life for each of the 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 (Part B only).

8.2.3.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.4.

For this protocol, the proportion of subjects who experience the following adverse events during the study therapy period will be estimated for each arm: gastrointestinal adverse events (vomiting, nausea, and diarrhea) and adverse events of elevated laboratory values that are reported as ECIs during the study therapy period.

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

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

8.2.3.3 Other Endpoints (Part B only)

1. 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 at Week 4, Week 8, Week 12 and the end of treatment visit for HIV-coinfected population.

2. Change from baseline in CD4+ T-Cell Counts at Week 4, Week 8, Week 12 and the end of treatment visit for HIV-coinfected population.

Note: Week 12 and end of treatment visit may be the same.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Per-Protocol (PP) population will serve as the primary population for the analysis of efficacy data in this study. The PP population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy endpoints. Potential violations that may result in the exclusion of a subject from the PP population include:

- Violations of specific inclusion/exclusion criteria:
 - The subject is infected with a non-GT 1a or GT 1b HCV infection at entry or during the course of the study, including a mixed GT infection (with a non-GT 1) or a non-typeable genotype (for Part A)
 - The subject is infected with a non-GT 1 HCV infection at entry or during the course of the study, including a mixed GT infection (with a non-GT 1) or a non-typeable genotype (for Part B)
- The subject met criteria for virologic failure but had undetectable MK-5172 levels and/or MK-8742 levels at one or more pharmacokinetic sampling timepoints temporally associated with the failure timepoint
- 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 including:
 - CYP3A4 inducers such as rifampin, carbamazepine and efavirenz,
 - P-gp inducers such as St. John's Wort,
 - 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 that will affect the composition of the PP population. These will be made prior to the final analyses, and they will be listed specifically in the CSR

A subject with important deviations from the protocol as described above at randomization will be excluded from the PP population. For subjects with important deviations from the

protocol as described above during course of the treatment, data obtained subsequent to the violation will be excluded from analysis.

A supportive analysis using the Full Analysis Set (FAS) population will be performed for the primary and key secondary efficacy endpoints. The FAS population consists of all randomized subjects who have received at least one dose of study treatment. The PP population is a subset of the FAS population.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the FAS and PP populations. 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 randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment they actually received.

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 Statistical Methods.

8.2.5 Statistical Methods

The approach to handling missing data is described in Section 8.2.5.1. A summary of the analysis strategy for efficacy variables is shown in [Table 17](#). Nominal p-values may be computed for some efficacy analyses as a measure of strength but no formal tests of hypotheses are planned in this study.

Statistical inference for safety analyses are described in 8.2.5.2.

8.2.5.1 Statistical Methods for Efficacy Analyses

Missing Values

There are 3 types of approaches to handle missing values for subjects who prematurely discontinue assigned treatment. Missing values means missing observations (rather than subjects).

- Observed Failure (OF) approach: Subjects who 1) discontinued assigned treatment early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD(q) during follow-up are considered as failures thereafter. Otherwise, any subject missing an HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point.
- Data As Observed (DAO) approach: During the treatment period, any subject missing an HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point.
- Missing=Failure (M=F) approach: Any subject missing an HCV RNA evaluation at any particular visit will be considered a non-responder for that visit. An exception will be made in the case where a missing on-treatment visit is immediately preceded and followed by a TND HCV RNA, where the missing value would be imputed to be TND as well. The same rule will be applied when the endpoint is defined using HCV RNA <25 IU/mL. When a missing value is flanked by TND RNA and HCV RNA <25 IU/mL, then HCV RNA <25 will be imputed.

If a subject does not have an HCV RNA evaluation on the last scheduled follow-up visit (i.e., no SVR₂₄) but has a value assigned to the 12-week follow-up visit, then SVR₁₂ will be used in place of SVR₂₄. If an earlier SVR assessment is missing but a later SVR assessment is available (e.g., a subject missed his 4-week follow-up visit, but returned for his 12-week follow-up visit), then the later result can be used to impute the missing earlier result.

For the endpoint of time to first achievement of undetectable HCV RNA, discontinued subjects who do not achieve undetectable HCV RNA will be considered censored at the discontinuation time point. Summary statistics will be provided to show the number of subjects discontinued due to virologic failures and AEs.

Proportions of Subjects With Virologic Responses

For the primary efficacy analysis to estimate the proportions of subjects achieving SVR₁₂, 95% confidence intervals of these rates will be calculated using the Clopper-Pearson method. The missing data approach of OF described above will be utilized for the primary analysis. The same method will be used to analyze all binary endpoints for all the treatment arms.

Sensitivity analyses will be performed for the primary endpoint using the FAS population with the M=F missing data approach.

Exploratory analyses will be performed to better understand the prognostic value of early endpoints (e.g., HCV viral response at Weeks 2 and 4) to predict later endpoints (SVR₁₂ and SVR₂₄).

Table 17 includes a summary of the key efficacy analyses.

Table 17 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 in each treatment arm	P	95% Confidence Interval (Clopper-Pearson)	PP	OF [‡]
Proportion of subjects achieving SVR ₁₂ in each treatment arm	S	95% Confidence Interval (Clopper-Pearson)	FAS	M=F [‡]
Secondary				
Time to first achievement of undetectable HCV RNA	P	Kaplan-Meier plot and summary statistics	PP	DAO
Proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA < 25 IU/mL at Week 2, Week 4, and Week 12, and achieving SVR ₄ , and SVR ₂₄ .	P	95% Confidence Interval (Clopper-Pearson)	PP	OF [‡]
[†] 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 DAO = Data as observed				

For Part B, each treatment arm will be assessed for the various endpoints within each subject population (TN non-cirrhotic, TN cirrhotic, Null-responders cirrhotic and non-cirrhotic, TN non-cirrhotic HIV co-infected). In addition, some subject populations may be combined for assessing treatment arms to provide increased precision, especially for comparing arms with and without ribavirin and for comparing different treatment durations.

HCV RNA Values

For analyses that require a specific numeric value for HCV RNA that may be below the limit of quantification (HCV RNA < 25 IU/mL,) or undetectable (HCV RNA TND), the following will be done to substitute for these values: (1) values < 25 IU/mL but not TND will have 24 IU/mL imputed; (2) values that are TND will be imputed with the value of 1 IU/mL. These imputations will be done solely for computational purposes.

Subject Virologic Failure: Futility, Rebound, Breakthrough, or Relapse

Summary statistics will be provided to describe the rates of occurrence of subject virologic futility, rebound, breakthrough, or relapse. Definitions for subject virologic futility, rebound, breakthrough, or 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 events and laboratory parameters.

The proportion of subjects with gastrointestinal adverse events (vomiting, nausea, and diarrhea), and adverse events of elevated laboratory values that are reported as ECIs during

the study therapy period will be provided per treatment arm along with corresponding 95% confidence intervals. For Part B, a confirmed detected HIV RNA (viral breakthrough) reported as an ECI would also be included in this analysis.

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 18](#)).

Missing values will be handled using the Data-As-Observed (DAO) approach.

Table 18 Analysis Strategy for Safety Parameters

Safety Endpoint [†]	95% CI	Descriptive Statistics
GI AEs (vomiting, nausea, diarrhea)	X	X
AEs of elevated laboratory values that are reported as ECIs	X	X
AE of a confirmed detected HIV RNA (viral breakthrough) reported as an ECI (Part B only)	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 SOC's		X
Change from Baseline Results (laboratory)		X
[†] Adverse events 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

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistic tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, 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, prior and concomitant therapies will be summarized by treatment using descriptive statistics for continuous or categorical variables, as appropriate. Summary statistics for the baseline efficacy measure (HCV RNA) will also be provided by treatment group.

Pharmacokinetic Analyses

Summary statistics for the concentrations of MK-5172, MK-8742, and RBV will be provided for each treatment group. PK/PD analysis will also be performed, which may include MK-5172, MK-8742, and RBV.

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.).

HCV genotyping is conducted using the Versant HCV genotype (LiPA) 2.0 manufactured by Innogenetics. In the US, the assay is distributed by Siemens.

IL28B Analyses and Other Genetic Analysis

Exploratory descriptive analyses will include demographic and selected baseline characteristics by *IL28B* genotype overall, as well as SVR₁₂ by *IL28B* genotype by treatment arm. Additional genetic analysis may be conducted to identify variations in HLA and ADME genes related to liver injury or other safety findings.

Patient-Reported Outcomes Measurement (Part B only)

Descriptive summary statistics will be provided for the change from baseline scores for each of the SF-36v2 eight health domains (Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health), and Physical Component Summary (PCS) and Mental Component Summary (MCS). These analyses will be conducted by treatment group and treatment duration at Week 4, and the end of treatment visit (which may be Week 12 or Week 18) or Early Discontinuation of Treatment Visit. Missing data will not be imputed and the analysis will be based on observed data only (DAO approach). These analyses will be based on the FAS population. No multiplicity adjustment will be applied.

Proportion of Subjects Who Develop HIV-1 Virologic Failure (Part B only)

For HIV co-infected subjects, the proportion of subjects who develop HIV-1 virologic failure (HIV-1 RNA ≥ 200 copies/mL using the Roche Cobas Ampliprep/Taqman v 2.0® assay confirmed on two 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. 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 (Part B only)

For HIV co-infected subjects, change from baseline in CD4+ T cell count will be estimated along with corresponding 95% (asymptotic) confidence intervals at Week 4, Week 8, and

Week 12, and at the end of treatment visit. Missing data will not be imputed and the analysis will be based on observed data only (DAO approach).

Association between baseline CD4+ T- Cell Count and SVR₁₂ (Part B only)

For HIV co-infected subjects, the mean and corresponding standard error of baseline CD4+T-cell counts will be estimated for the subjects with SVR₁₂ vs. the subjects who did not achieve SVR₁₂.

8.2.6 Multiplicity

During the course of the study, periodic efficacy and safety analyses will be performed for programmatic decisions that will not change the conduct of the current study. There will be no multiplicity adjustments made to account for the periodic assessments in the final analysis of this estimation study.

8.2.7 Sample Size and Power Calculations

8.2.7.1 Efficacy Analysis

Part A in this estimation study will randomize approximately 24 subjects in each treatment arm with RBV and 12 subjects in the treatment arm without RBV. Assuming a protocol violation rate of 10%, the PP population will include 22 subjects per arm in the arms with RBV and 11 subjects in the arm without RBV. In Part B, 30 subjects from different subject populations will be randomized into various treatment regimens. Assuming a protocol violation rate of 10%, the PP population will include 27 subjects. [Table 19](#) shows two-sided 95% confidence intervals for SVR₁₂ under varying assumptions of the number of successes seen for the PP population. Note that these intervals are not symmetric around the point estimate.

Table 19 Two-Sided 95% Confidence Interval[‡] for SVR₁₂; Assuming Various Number of Successes (Per-Protocol Population)

	Observed Number of Successes (%)	Two-Sided 95% Confidence Interval [‡]
Part A: PP population in arms with RBV = 22	10 (45.5%)	(25.3, 66.9)
	12 (54.5%)	(33.1, 74.7)
	14 (63.6%)	(41.7, 82.1)
	16 (72.7%)	(50.8, 88.7)
	18 (81.8%)	(60.8, 94.4)
	20 (90.9%)	(72.0, 98.7)
Part A: PP population in arm without RBV = 11	7 (63.6%)	(30.8, 89.1)
	8 (72.7%)	(39.0, 94.0)
	9 (81.8%)	(48.2, 97.7)
	10 (90.9%)	(58.7, 99.8)
Part B: PP population in any arm within a subject population = 27	17 (63.0%)	(42.4, 80.6)
	19 (70.4%)	(49.8, 86.3)
	21 (77.8%)	(57.7, 91.4)
	23 (85.2%)	(66.3, 95.8)
	25 (92.6%)	(75.7, 99.1)
	27 (100%)	(87.2, 100)
[‡] Based on the Clopper-Pearson method		

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 8.2.3.2 of this document. This calculation is based on the exact binomial method proposed by Clopper and Pearson (1934). [Table 20](#) gives the upper bound of the two-sided 95% Clopper-Pearson exact confidence interval for the true proportion of subjects with a particular adverse event corresponding to various observed numbers of subjects with such adverse event in samples of 24 or 12 subjects. For example, if a particular adverse event is not observed in any of the 24 subjects in an arm, then we can conclude with 95% confidence that the true proportion is no more than 14.2%. Likewise, if a particular adverse event is not observed in any of the 12 subjects in an arm, then we can conclude with 95% confidence that the true proportion is no more than 26.5%.

Table 20 Upper Bound of the Two-Sided 95% Confidence Interval for the True Proportion of Subjects With an AE

n	Observed Number of Subjects With AE	Percentage (%) of Subjects With AE (Upper Bound of the 95% CI)
(Part A) 24	0	0.0 (14.2)
	1	4.2 (21.2)
	2	8.3 (27.0)
	3	12.5 (32.4)
	5	16.7 (37.4)
	8	33.3 (55.3)
(Part A) 12	0	0.0 (26.5)
	1	8.3 (38.5)
	3	25.0 (57.2)
(Part B) 30	0	0.0 (11.6)
	3	10.0 (26.5)
	6	20.0 (38.6)
	9	30.0 (49.4)
	12	40.0 (59.4)
	15	50.0 (68.7)

In Protocol 003, the observed incidence of ALT and AST elevations >2-fold ULN late in the course of therapy for low doses of MK-5172 (100- and 200- mg QD) was 3% to 4% (Section 4.2.2). Using this as a basis, the probability of observing 1 or more of these events in any treatment group in this study given sample sizes of n= 12, 24 or 30 per arm are as follows (Table 21):

Table 21 Probability of Observing Late Transaminase Elevations

True rate of late transaminase elevations	Probability of observing at least one case		
	Part A (n=12)	Part A (n=24)	Part B (n=30)
2%	0.22	0.38	0.45
4%	0.39	0.62	0.71
6%	0.52	0.77	0.84

8.2.8 Subgroup Analyses and Effects of Baseline Factors

To determine whether the response is consistent across various subgroups, 95% CIs for SVR₁₂ will be estimated within each category of the following classification variables:

- Sex (female, male)
- GT Part A; (1a vs 1b) Part B: (1a vs 1 non-a)
- *IL28B* CC genotype vs. non-CC genotype
- HCV RNA at Screening , low (\leq 800,000 IU/mL) versus high ($>$ 800,000 IU/mL)
- Stage of fibrosis

The consistency of the response will be assessed descriptively using summary statistics for each category of the classification variables listed above.

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 22](#).

Table 22 Product Descriptions

Product Name & Potency	Dosage Form
Part A:	
MK-5172 100mg	Tablet
MK-8742 10mg or Placebo	Capsule
Ribavirin (RBV) 200mg	Capsule
Peginterferon alfa-2b (Peg-IFN)- 50, 80, 120 Or 150 µg/0.5mL	Single Use Vial with diluent or REDIPEN TM
Part B:	
MK-5172 100mg	Tablet
MK-8742 10mg	Capsule
MK-8742 50mg (formulation 2)	Tablet
Ribavirin (RBV) 200mg	Capsule
Peginterferon alfa-2b (Peg-IFN)- 50, 80, 120 Or 150 µg/0.5mL	Single Use Vial with diluent or REDIPEN TM

9.2 Packaging and Labeling Information

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

For Part A, subjects will receive open label bottles of MK-5172, and blinded bottles of MK-8742 and/or placebo at monthly dispensing visits. Subjects will receive open label RBV bottles at monthly dispensing visits for RBV containing arms.

Subjects in arms that have undergone treatment arm modification will also receive open label bottles of RBV, and open label Peginterferon alfa-2b kits at monthly dispensing visits. Open label RBV and Peginterferon alfa-2b can be sourced locally if needed.

For Part B, subjects will receive open label bottles of MK-5172 and MK-8742 at monthly dispensing visits. Subjects will receive open label RBV bottles at monthly dispensing visits for RBV containing arms.

Subjects in arms that have undergone treatment arm modification will also receive open label bottles of RBV, and open label Peginterferon alfa-2b kits at monthly dispensing visits.

9.3 Clinical Supplies Disclosure

The central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask drug identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign drug 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:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;

- curriculum vitae or other summary of qualifications and credentials; and
- 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.

10.2 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 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 discarding 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 by the Sponsor.

10.7 Publications

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

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

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

11.0LIST OF REFERENCES

1. Report of a WHO Consultation Organized in Collaboration with the Viral Hepatitis Prevention Board. Global surveillance and control of hepatitis C. J of Hepatology 1999; 6:35-47.
2. Leung, NWY. Management of viral hepatitis C. Gastroenterology-Hepatology. 2002;17: S146- S154.
3. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet. 2001; 358:958-65.
4. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195-206.

5. McHutchison JG, Everson GT., Gordon SC, Jacobson IM: Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ., PROV. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J Med.* 2009; 360 (18): 1827- 1838.
6. Lawitz E, Poordad F, Kowdley KV, Jensen D, Cohen DE, Siggelkow S, Wikstrom K, Larsen L, Menon RM, Podsadecki T, Bernstein B A 12-Week Interferon-Free Regimen of ABT-450/r, ABT-072, and Ribavirin was Well Tolerated and Achieved Sustained Virologic Response in 91% Treatment-Naïve HCV *IL28B*-CC Genotype-1-Infected Subject . *Journal of Hepatology*; v:56 p:S7.
7. Suzuki F, Ikeda K, Toyota J, Karino Y, Ohmura T, Chayama K, Takahashi S, Kawakami Y, Ishikawa H, Watanabe H, Hu W, McPhee F, Hughes E, Kumada H. Dual Oral Therapy with the NS5A Inhibitor Daclatasvir (BMS-790052) and NS3 Protease Inhibitor Asunaprevir (BMS-650032) in HCV Genotype 1b-Infected Null Responders or Ineligible/Intolerant to PegInterferon/Ribavirin. *Journal of Hepatology*; v:56 p:S7-S8.
8. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse A, Mullhaupt B, Schuchmann M, Bourliere M, Buti M, Roberts S, Gane E, Stern JO, Kukulj G, Dai L, Bocher WO, Mensa SVR4 and SVR12 with an Interferon-Free Regimen of BI201335 and BI207127, +/- Ribavirin, in Treatment-Naïve Patients with Chronic Genotype-1 HCV Infection: Interim Results of SOUND-C2 . *Journal of Hepatology*; v:56 p:S45.
9. Gane EJ, Stedman CA, Hyland RH, Sorensen RD, Symonds WT, Hindes RG, Berrey MM. ELECTRON: Once Daily PSI-7977 plus RBV in HCV GT1/2/3. *Journal of Hepatology*; v:56 p:S438-S439.
10. Poordad F, Lawitz E, Kowdley KV, Everson GT, Freilich B, Cohen D, Siggelkow S, Heckaman M Menon R, Matias TP, Podsadecki T Bernstein B. 12-Week Interferon-Free Regimen of ABT-450/r+ABT-333+Ribavirin Achieved SVR12 in More Than 90% of Treatment-Naïve HCV Genotype-1-Infected Subjects and 47% of Previous Non-Responders . *Journal of Hepatology*; v:56 p:S549-S550.
11. Pawlotsky JM, Sarin SK, Foster G, Peng CY, Rasenack J, Flisiak R, Piratvisuth T, Wedemeyer H, Chuang WL, Zhang WM, Naoumov NV. Alisporivir plus Ribavirin is highly effective as interferon-free or interferon-add-on regimen in previously untreated HCV-GT2 or GT3 patients: SVR12 results from VITAL-1 Phase 2b study . *Journal of Hepatology*; v:56 p:S553.
12. Gane EJ, Pockros P, Zeuzem S, Marcellin P, Shikhman A, Bernaards C, Yetzer ES, Shulman N, Tong X, Najera I, Bertasso A, Hammond J, Stancic S. Interferon-free Treatment with a Combination of Mericitabine and Danoprevir/r with or without Ribavirin in Treatment-Naïve HCV Genotype-1-infected patients. *Journal of Hepatology*; v:56 p:S555-S556.
13. Sulkowski M, Gardiner D, Lawitz E, Hineostroza F, Nelson D, Thuluvath P, Rodriguez-Torres M, Lok A, Schwartz H, Reddy KR, Eley T, Wind-Rotolo M, Huang SP, Gao M,

McPhee F. Potent Viral Suppression with All-Oral Combination of Daclatasvir (NS5A Inhibitor) and GS-7977 (NS5B Inhibitor), +/- Ribavirin, in Treatment-Naïve Patients with Chronic HCV GT1, 2, or 3. *Journal of Hepatology*; v:56 p:S560.

14. Lok, A, Gardiner, D., Lawitz, E., Martorell, C., Everson, G., Ghalib, R., Reindollar, R., Rustgi, V., McFhee, F., Wind-Rotolo, M., Persson, A., Zhu, K., Dimitrova, D., Eley, T., Guo, T., Grasela, D., Pasquinelli, C. Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1. *N. Engl. J. Med.* 366, 216-224 (2012).
15. Reddy, K., Nelson, D., Zeuzem, S. Ribavirin: Current role in the optimal clinical management of chronic hepatitis C. *Journal of Hepatology*, v50 p:402-411 (2009).
16. Fried, M., Shiffman, M., Reddy, K., Smith, C., Marinos, G., Goncales, F., Haussinger, D., Diago, M., Carosi, G., Dhumeaux, D., Craxi, A., Lin, A., Hoffman, J., Yu, J. N. Peginterferon Alfa-2a Plus Ribavirin for Chronic Hepatitis C Virus Infection. *Engl. J. Med.* 347, 975-982 (2002).
17. Feld, J., Hoofnagle, J. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* 2005; 436:967-972.
18. Bergamini, A., Bolacchi, F., Cepparulo, M., Demin, F., Uccella, I., Bongiovanni, B., Ombres, D., Angelico, F., Liuti, A., Hurtova, M., Francioso, S., Carvelli, C., Cerasari, G., Angelico, M., Rocchi, G. Treatment with ribavirin and interferon- reduces interferon-expression in patients with chronic hepatitis C. *Clin Exp Immunol* 2001; 123:459-464.
19. Fujita, N., Kaito, M., Tanaka, H., Horiike, S., Urawa, N., Sugimoto, R., Konishi, M., Watanabe, S., Adachi, Y. Hepatitis C virus free-virion and immune-complex dynamics during interferon therapy with and without ribavirin in genotype-1b chronic hepatitis C patients. *Journal of Viral Hepatitis*, 2006, 13, 190-198.
20. Kowdley KV, Lawitz E, Poordad F, et al. A 12-week interferon-free treatment regimen with ABT-450/r, ABT-267, ABT-333, and ribavirin achieves SVR12 rates (observed data) of 99% in treatment-naïve patients and 93% in prior null responders with HCV genotype 1 infection. Program and abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, 2012; Boston, Massachusetts. Abstract LB-1
21. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naïve patients chronically infected with HCV genotype 1, 2, or 3. Program and abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, 2012; Boston, Massachusetts. Abstract LB-2.
22. Everson GT, Sims KD, Rodriguez-Torres M, et al. An interferon-free, ribavirin-free 12-week regimen of daclatasvir (DCV), asunaprevir (ASV), and BMS-791325 yielded SVR4 of 94% in treatment-naïve patients with genotype (GT) 1 chronic hepatitis C virus (HCV)

infection. Program and abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, 2012; Boston, Massachusetts. Abstract LB-3.

23. Lahser F, Liu R, Bystol K, et.al. A Combination Containing MK-5172 (HCV NS3 protease inhibitor) and MK-8742 (HCV NS5A inhibitor) Demonstrates High Barrier to Resistance in HCV Replicon.s Program and abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, 2012; Boston, Massachusetts. Abstract 87.
24. S. Pol, G. Everson, R. Ghalib, V. Rustgi, C. Martorell, H. Tatum, J. Lim, C. Hezode, U. Diva, P.D. Yin, and R. Hindes . Once-daily NS5A Inhibitor (BMS-790052) Plus Peginterferon-alpha-2a And Ribavirin Produces High Rates of Extended Rapid Virologic Response In Treatment-naïve HCV-genotype 1 Subjects: Phase 2a Trial - Bristol-Myers Squibb Study AI444014. European Association for the Study of the Liver, Amsterdam, The Netherlands, 25 April 2013.
25. Company Report May 2, 2013: Gilead Reports Interim Data From Phase 2 LONESTAR Study
26. Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53.
27. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson D, Zeuzem S, et al. Safety and efficacy of interferon-free regimens Of ABT-450/r, ABT-267, ABT-333 +/- ribavirin in patients with chronic HCV GT1 infection: results from the aviator study. EASL 48th Annual Meeting; 2013 Apr 24. The Netherlands, Amsterdam, 2013.
28. Zeuzem S, Soriano V, Asselah T, Bronowicki J-P, Lohse AW, Müllhaupt B, et al. Interferon (IFN)-free combination treatment with the HCV NS3/4A protease inhibitor faldaprevir (BI 201335) and the non-nucleoside NS5B inhibitor BI 207127 ± ribavirin: Final results of sound-C2 and predictors of response. 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 Nov 9. Boston, MA, 2012.
29. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;1-11.
30. Lawitz E, Ghalib R, Rodriguez-Torres M, Younossi Z, Corregidor A, Jacobson I, et al. Suppression of viral load through 4 Weeks post-treatment results of a once-daily regimen of simeprevir + sofosbuvir with or without ribavirin in hepatitis C virus GT 1 null responders (Paper #155LB). 2013 Mar 3. Atlanta, GA, 2013.
31. Sulkowski MS. Hepatitis C virus-human immunodeficiency virus coinfection. Liver Int. 2012 Feb;32 Suppl 1:129-34.

32. McHutchison JG, Everson GT., Gordon SC, Jacobson IM: Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ., PROV. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J Med.* 360 (18): 1827- 1838, 2009.
33. D. T. Dieterich, V. Soriano, K. E. Sherman, P. M. Girard, J. K. Rockstroh, J. Henshaw, R. Rubin, M. Bsharat, N. Adda, M. S. Sulkowski. Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Co-infected Patients: SVR12 Interim Analysis. 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012). Seattle, WA. March 5-8, 2012.
34. D. T. Dieterich, V. Soriano, P. Y. Kwo, E. J. Lawitz, J. McCone, E. R. Schiff, J. M. Vierling, D. Pound, M. N. Davis, J. S. Galati, S. C. Gordon, N. Ravendhran, L. Rossaro, F. H. Anderson, I. M. Jacobson, R. Rubin, K. Koury, L. D. Pedicone, C. A. Brass, E. Chaudhri, J. K. Albrecht. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 376: 705-716, 2010.
35. M. Sulkowski, S. Pol, C. Cooper, H. Fainboim, J. Slim, A. Rivero, M. Laguno, S. Thompson, J. Wahl, W. Greaves. Boceprevir + Pegylated Interferon + Ribavirin for the Treatment of HCV/HIV-coinfected Patients: End of Treatment (Week 48) Interim Results. 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012). Seattle, WA. March 5-8, 2012.
36. Gravitz L. Introduction: a smouldering public-health crisis. *Nature.* 2011 Jun 8;474(7350):S2-4
37. Bronowicki J-P, Hezode C, Bengtsson L, Pol S, Bourliere M, Serfaty L, de Ledinghen V, Tran A, Benhamou Y., Grange J-D, Mathurin P, Marcellin P, Trepo C, Zarski J-P, Seepersaud S, Kelliher K, Botfield M, Pawlotsky J-M. 100% SVR in *IL28B* CC patients treated with 12 weeks of telaprevir, peginterferon, and ribavirin in the PROVE2 trial. *Journal of Hepatology*, Volume 56, Supplement 2, April 2012, Pages S430-S431.
38. Gane, EJ, Stedman CA, Hyland RH, Sorensen RD, Symonds WT, Hindes RG, Berrey MM ELECTRON: Once Daily PSI-7977 plus RBV in HCV GT1/2/3. *Journal of Hepatology*; v:56 p:S438-S439.
39. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N. Engl. J. Med.* 361, 580-593 (2009).
40. Alberti A. Impact of a sustained virological response on the long-term outcome of hepatitis C. *Liver Int.* 2011 Jan;31 Suppl 1:18-22.

41. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclerc L, Castelnau C, Giuly N, El Ray A, Cardoso AC, Moucari R, Asselah T, Marcellin P. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology*. 2010 Apr;51(4):1122-6.
42. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461(7262):399-401
43. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. *IL28B* is associated with response to chronic hepatitis C interferon-[alpha] and ribavirin therapy. *Nat Genet* 2009; 41(10):1100-4, 447.
44. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of *IL28B* with response to pegylated interferon-[alpha] and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; 41(10):1105-9, 449.
45. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus. *Nature* 2009; 461(7265):798-801.
46. Spiegel BMR, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology* 2005; 41:790-800.
47. Foster GR. Quality of life considerations for patients with chronic hepatitis C. *Journal of Viral Hepatitis* 2009; 16:605–611.
48. Ware JE Jr, Bayliss MS, Mannocchia M, Davis GL and the International Hepatitis Interventional Therapy Group. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. *Hepatology* 1999; 30:550-555.
49. McHutchison JG, Ware JE Jr, Bayliss MS, Pianko S, Albrecht JK, Cort S, Yang I, Neary MP and the Hepatitis Interventional Therapy Group. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. *J Hepatology* 2001; 34:140-147.
50. Hassanein T, Cooksley G, Sulkowski M, Smith C, Marinos G, Lai MY, Pastore G, Trejo-Estrada R, Horta e Vale A, Wintfeld N, Green J. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. *J Hepatology* 2004; 40: 675-681.
51. Rasenack J, Zeuzem S, Feinman SV, Heathcote EJ, Manns M, Yoshida EM, Swain MG, Gane E, Diago M, Revicki DA, Lin A, Wintfeld N, Green J. Peginterferon alfa-2a (40kD) [Pegasys®] improves HR-QOL outcomes compared with unmodified interferon alfa-2a [Roferon®-A] in patients with chronic hepatitis C. *Pharmacoeconomics* 2003; 21: 341-349.

52. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. *Seminars In Liver Disease* 1999;19 Suppl 1: 77-85.
53. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Annals of Internal Medicine* 2013; 158: 807-820.
54. Foucher J, Chanteloup E, Vergniol J, Caste´ra L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Le´dinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006;55:403–408.