Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study

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Summary

Background Chronic hepatitis C virus (HCV) infection in patients with stage 4–5 chronic kidney disease increases the risk of death and renal graft failure, yet patients with hepatitis C and chronic kidney disease have few treatment options. This study assesses an all-oral, ribavirin-free regimen in patients with HCV genotype 1 infection and stage 4–5 chronic kidney disease.

Methods In this phase 3 randomised study of safety and observational study of efficacy, patients with HCV genotype 1 infection and chronic kidney disease (stage 4–5 with or without haemodialysis dependence) were randomly assigned to receive grazoprevir (100 mg, NS3/4A protease inhibitor) and elbasvir (50 mg, NS5A inhibitor; immediate treatment group) or placebo (deferred treatment group) once daily for 12 weeks. Randomisation was done centrally with an interactive voice response system. An additional cohort of patients who were not randomised received the same regimen open-label and underwent intensive pharmacokinetic sampling. The primary efficacy outcome was a non-randomised comparison of sustained virological response at 12 weeks (SVR12) after the end of therapy for the combined immediate treatment group and the pharmacokinetic population with a historical control. The primary safety outcome was a randomised comparison between the immediate treatment group and the deferred treatment group. After 4 weeks of follow-up (study week 16), unmasking occurred and patients in the deferred treatment group received grazoprevir and elbasvir. The primary efficacy hypothesis was tested at a two-sided significance level (type I error) of 0·05 using an exact test for a binomial proportion. Safety event rates were compared between immediate treatment and deferred treatment groups using the stratified Miettinen and Nurminen method with baseline dialysis status as the strata. The study is registered at ClinicalTrials.gov, number NCT02092350.

Findings 224 patients were randomly assigned to the immediate treatment group with grazoprevir and elbasvir (n=111) or the deferred treatment group (n=113), and 11 were assigned to the intensive pharmacokinetic population. Overall, 179 (76%) were haemodialysis-dependent, 122 (52%) had HCV genotype 1a infection, 189 (80%) were HCV treatment-naive, 14 (6%) were cirrhotic, and 108 (46%) were African American. Of the 122 patients receiving grazoprevir and elbasvir, six were excluded from the primary efficacy analysis for non-virological reasons (death, lost-to-follow-up [n=2], non-compliance, patient withdrawal, and withdrawal by physician for violent behaviour). No patients in the combined immediate treatment group and intensive pharmacokinetic population and five (4%) in the deferred treatment group discontinued because of an adverse event. Most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving active and placebo drugs. SVR12 in the combined immediate treatment group and intensive pharmacokinetic population was 99% (95% CI 95·3–100·0; 115/116), with one relapse 12 weeks after end of treatment when compared with a historical control of 45%, based on meta-analyses of interferon-based regimens used in clinical trials of patients infected with HCV who are on haemodialysis.

Interpretation Once-daily grazoprevir and elbasvir for 12 weeks had a low rate of adverse events and was effective in patients infected with HCV genotype 1 and stage 4–5 chronic kidney disease.

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Introduction

Hepatitis C infection accelerates the decline in kidney function in patients with chronic kidney disease and increases mortality among patients on haemodialysis[1] compared with patients not infected with hepatitis C on dialysis.[2–6] Studies among kidney transplant patients show infection with hepatitis C also has an adverse effect on patient and graft survival.[7–9] These data suggest that clearance of hepatitis C infection among patients with stage 4–5 chronic kidney disease (estimated glomerular

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Research in context

Evidence before this study

Patients with stage 4–5 chronic kidney disease and hepatitis C infection have few treatment options for hepatitis C virus (HCV). At the time this study was designed, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended treatment was interferon or pegylated interferon. Some investigators also explored adding ribavirin to pegylated interferon. Unfortunately, these regimens are associated with treatment-limiting toxic effects and suboptimum efficacy. We searched PubMed for clinical trials published before Jan 31, 2015, describing the treatment of hepatitis C in patients with advanced chronic kidney disease. Although this search returned a total of 97 relevant articles, the data on this subject are summarised most concisely in a series of meta-analyses. The most recent of these meta-analyses (based on data from 28 clinical trials done between 1990 and 2006, and including 645 patients) suggests that interferon or pegylated interferon monotherapy was associated with a sustained virological response (SVR) in about one in three patients when treated for 16–48 weeks, whereas about 20–25% of patients did not complete treatment. In the past 5 years, the introduction of direct-acting antiviral therapies has dramatically improved treatment options for patients with hepatitis C. High rates of SVR, coupled with improved tolerability, are now available to many patients with HCV infection; however, in our literature review, we were unable to identify any published studies of direct-acting antiviral therapies in patients with advanced chronic kidney disease. Thus, patients with hepatitis C and stage 4–5 chronic kidney disease remain underserved by current direct-acting antiviral hepatitis C treatment regimens.

Added value of this study

This study is the first phase 3 study to assess an interferon-free, ribavirin-free, all-oral treatment regimen for patients with HCV infection and advanced (stage 4–5) chronic kidney disease. Patients receiving grazoprevir plus elbasvir for 12 weeks had a low rate of adverse events compared with a deferred treament group and achieved a 99% SVR12 compared with a historical control.

Implications of all the available evidence

Grazoprevir and elbasvir is an investigational medicine and is not approved for the treatment of HCV infection. However, data from the present study suggest that the availability of a grazoprevir and elbasvir regimen for patients with stage 4–5 chronic kidney disease could represent a marked improvement in treatment for this significantly underserved patient group.

filtration rate [eGFR] ≤29 mL/min per 1·73 m² or on dialysis), especially those who are candidates for kidney transplantation, is of great importance.

Treatment options for patients with hepatitis C infection and stage 4–5 chronic kidney disease remain suboptimum. Approved all-oral therapies are not ideal regimens because they contain drugs whose metabolites are cleared by the kidney (such as sofosbuvir) or because they need co-administration with ribavirin, which is associated with anaemia.

Grazoprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and elbasvir, an NS5A protein inhibitor, are undergoing clinical assessment as a once-daily regimen for the treatment of HCV genotype 1, 4, and 6 infections.[10–14] Phase 1 studies have shown that less than 1% of grazoprevir and elbasvir are renally excreted, and that dose adjustments of grazoprevir or elbasvir are not needed in the setting of non-dialysis-dependent stage 4–5 chronic kidney disease and dialysis-dependent stage 5 chronic kidney disease.[15] C-SURFER (Hepatitis C: Study to Understand Renal Failure's Effect on Responses) is the first phase 3 study of an all-oral HCV regimen in patients with stage 4–5 chronic kidney disease and HCV genotype 1 infection. The aims of the study were to assess the efficacy, safety, and tolerability of grazoprevir plus elbasvir in patients with HCV genotype 1 infection and with chronic kidney disease stage 4–5.

Methods

Study design and participants

C-SURFER is a multicentre, phase 3, double-blind study comprising a randomised study of safety and an observational study of efficacy. Adult patients infected with HCV genotype 1 and with chronic kidney disease (stage 4–5 with or without haemodialysis dependence) were selected for inclusion. Complete eligibility criteria are provided in the study protocol. Chronic kidney disease stages 4 and 5 were defined based on eGFR (according to the Modification of Diet in Renal Disease [MDRD]-4 equation)[16] 15–29 mL/min per 1·73 m² and less than 15 mL/min per 1·73 m² or on dialysis, respectively. Patients were either treatment-naive for HCV or had previously received an interferon regimen. Liver staging was based on biopsy within 24 months of enrolment; Fibroscan within 12 months of enrolment; or a combination of Fibrotest score greater than 0·75 and an AST to platelet ratio of greater than 2.[17–19]

The study was done at 68 centres in the USA, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, Netherlands, Spain, and Sweden in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines, and other regulations governing clinical study conduct. The protocol was approved by an independent ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to receive grazoprevir 100 mg and elbasvir 50 mg once daily (immediate treatment group) or placebo (deferred treatment group) for 12 weeks. 4 weeks after the end of treatment (week 16), patients and site personnel were unmasked, and those randomised to the deferred

treatment group received grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks (appendix). An additional cohort received open-label grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks and underwent intensive pharmacokinetic sampling. Patients were recruited on a voluntary basis at study sites with expertise in conducting pharmacokinetic studies.

Randomisation for the safety study was done centrally using an interactive voice response system and stratified according to dialysis (yes/no) and presence of diabetes (yes/no) with a block size of 4. Grazoprevir, elbasvir, and placebos were manufactured to preserve masking (confirmed as visually identical) and packaged identically. All clinical supplies were provided by Merck & Co., Inc. Patients, investigators, and site personnel were masked to treatment assignment.

Procedures

Blood samples for assessment of HCV RNA were collected at baseline, at treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12, and at 4, 12, and 24 weeks after end of treatment. Plasma HCV RNA concentrations were measured using Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 (Roche, Indianapolis, IN, USA) with a lower limit of quantification of less than 15 IU/mL. Blood samples for assessment of viral resistance were collected at baseline from all patients, and at virological failure for patients with HCV RNA greater than 1000 IU/mL who met criteria for virological failure. For patients on haemodialysis, laboratory sampling was done before dialysis.

See Online for appendix

Patients underwent routine laboratory testing, electrocardiograms, and symptom-directed physical examinations at baseline, and during, and after completion of treatment. Adverse events were graded according to a standardised scale (study protocol, appendix).

The deferred treatment group served as an internal control for potential safety signals in the immediate treatment group. Active therapy in the deferred treatment group is ongoing: data described herein are observations from the initial placebo treatment period plus 14 days (results of the deferred open-label treatment with grazoprevir and elbasvir will be presented elsewhere). All patients will be followed for 24 weeks after completion of therapy.

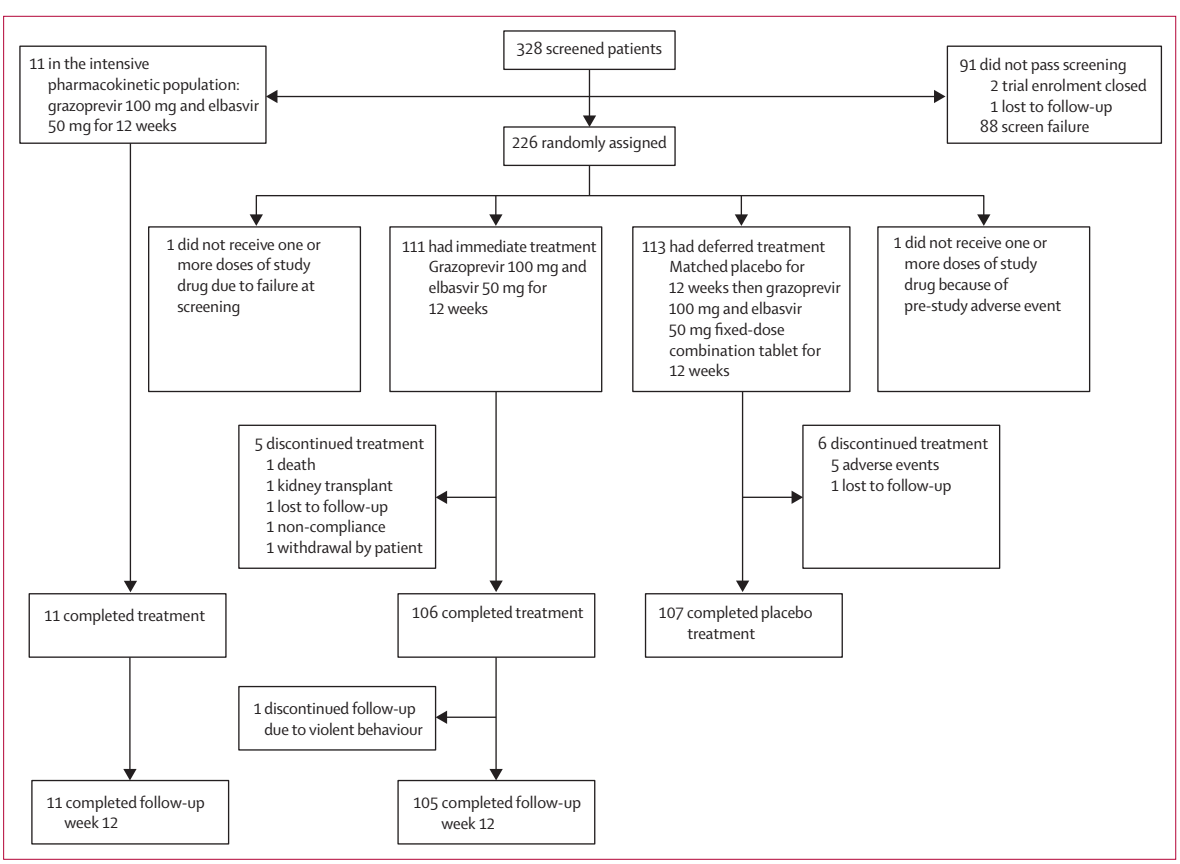

Figure 1: **Trial profile**

For the deferred treatment group, this figure does not show two deaths (pneumonia and unknown cause of death) that occurred after completion of treatment. In total, there were three deaths in the deferred treatment group (aortic aneurysm, pneumonia, and unknown cause of death): one patient discontinued due to an adverse event and then died (listed as discontinued). One patient in the immediate-treatment group discontinued study drug due to a kidney transplant at treatment week 4 but was not excluded from the modified full analysis set population because the patient continued to participate in the study, remaining in follow-up despite early discontinuation of the study drug.

	Grazoprevir and elbasvir pharmacokinetic population (n=11)	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)	Total (n=235)
Sex				
Male	11 (100%)	81 (73·0%)	80 (70·8%)	172 (73·2%)
Female	0	30 (27·0%)	33 (29·2%)	63 (26·8%)
Age, years	58·2 (6·8)	56·5 (9·1)	55·2 (10·1)	56·0 (9·5)
Race				
White	6 (54·5%)	55 (49·5%)	48 (42·5%)	109 (46·4%)
African-American	5 (45·5%)	50 (45·0%)	53 (46·9%)	108 (46·0%)
Asian	0	5 (4·5%)	9 (8·0%)	14 (6·0%)
Other	0	1 (0·9%)	3 (2·7%)	4 (1·7%)
Ethnic origin				
Hispanic–Latino	2 (18·2%)	11 (9·9%)	14 (12·4%)	27 (11·5%)
Not Hispanic–Latino	9 (81·8%)	98 (88·3%)	99 (87·6%)	206 (87·7%)
Other	0	2 (1·8%)	0	2 (0·9%)
HCV genotype				
1a	10 (90·9%)	53 (47·7%)	59 (52·2%)	122 (51·9%)
1b	1 (9·1%)	58 (52·3%)	53 (46·9%)	112 (47·7%)
1 other	0	0	1 (0·9%)	1 (0·4%)
IL28B				
CC	2 (18·2%)	30 (27·0%)	30 (26·5%)	62 (26·4%)
Non-CC	9 (81·8%)	79 (71·2%)	83 (73·5%)	171 (72·8%)
Missing	0	2 (1·8%)	0	2 (0·9%)
Cirrhosis				
No	11 (100·0%)	104 (93·7%)	106 (93·8%)	221 (94·0%)
Yes	0	7 (6·2%)	7 (6·2%)	14 (6·0%)
Hepatitis fibrosis stage				
F0–F2	11 (100%)	76 (68·5%)	76 (67·3%)	163 (69·4%)
F3	0	13 (11·7%)	15 (13·3%)	28 (11·9%)
F4	0	7 (6·3%)	7 (6·2%)	14 (6·0%)
Other*	0	15 (13·5%)	15 (13·3%)	30 (12·8%)
Baseline HCV RNA				
≤800 000 IU/mL	3 (27·3%)	50 (45·0%)	47 (41·6%)	100 (42·6%)
>800 000 IU/mL	8 (72·7%)	61 (55·0%)	66 (58·4%)	135 (57·4%)
HCV treatment history				
Naive	10 (90·9%)	91 (82·0%)	88 (77·9%)	189 (80·4%)
Experienced	1 (9·1%)	20 (18·0%)	25 (22·1%)	46 (19·6%)
Dialysis status				
On dialysis	6 (54·5%)	86 (77·5%)	87 (77·0%)	179 (76·2%)
Not on dialysis	5 (45·5%)	25 (22·5%)	26 (23·0%)	56 (23·8%)
Diabetes status				
Diabetes	6 (54·5%)	38 (34·2%)	36 (31·9%)	80 (34·0%)
No diabetes	5 (45·5%)	73 (65·8%)	77 (68·1%)	155 (66·0%)
Chronic kidney disease stage				
4	4 (36·4%)	18 (16·2%)	22 (19·5%)	44 (18·7%)
5	7 (63·6%)	93 (83·8%)	91 (80·5%)	191 (81·3%)

(Table 1 continues on next page)

An external data monitoring committee met when 50% of patients had completed treatment week 4 or discontinued before treatment week 4 and again when all patients had completed treatment week 8 or discontinued before treatment week 8. After each meeting, it was recommended the study continue as planned.

Outcomes

The primary efficacy outcome was a non-randomised comparison of sustained virological response at 12 weeks after the end of therapy (SVR12) for patients in the immediate treatment group and intensive pharmacokinetic population versus historical control patients with a reference SVR12 of 45% (appendix). Relapse was defined as detectable HCV RNA following the end of therapy, after undetectable at end of treatment. The primary safety outcome was a comparison between the randomised immediate treatment and deferred treatment groups. Tier 1 safety events were defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 500 IU/L; ALT or AST greater than three times the baseline and greater than 100 IU/L; alkaline phosphatase greater than three times the upper limit of normal. Tier 2 safety events were defined as patients with one or more adverse events, a drug-related adverse event, a serious adverse event, a serious renal adverse event, a serious and drug-related adverse event, an adverse event leading to discontinuation from treatment, and changes in renal function (increasing dialysis frequency in patients on haemodialysis at baseline, initiation of maintenance haemodialysis in patients not on haemodialysis at baseline, or an increase in chronic kidney disease stage). Tier 2 safety parameters also included change from baseline in serum creatinine, blood urea nitrogen, and eGFR in patients not receiving haemodialysis at baseline. Pharmacokinetic data are not reported here. Secondary endpoints not reported here are the SVR24 for the immediate treatment group and SVR12 for the active treatment phase of the deferred group.

Statistical analysis

According to the primary hypothesis, patients receiving grazoprevir and elbasvir in the immediate treatment group and intensive pharmacokinetic population will achieve an SVR12 rate higher than the reference rate of 45% (appendix). This value is based on a meta-analysis indicating an SVR rate of 39% in patients with stages 3–5 chronic kidney disease receiving interferon monotherapy[20] and an SVR of 40% in patients with HCV genotype 1 infection without renal disease receiving peginterferon and ribavirin.[21] The primary hypothesis was tested at a two-sided significance level (type I error) of 0·05 using an exact test for a binomial proportion. A 95% CI was also constructed for the SVR12 rate using the Clopper-Pearson method on non-randomised populations.

The modified full analysis set served as the primary population for the analysis of efficacy, and included patients assigned to the immediate treatment group or assigned to the intensive pharmacokinetic group, excluding those who failed to receive one or more doses

of drug, died, or discontinued from the study early for reasons unrelated to hepatitis C treatment. A secondary analysis including all patients who received at least one dose of study drug (full analysis set) was also done.

Target enrolment was 105 patients in each of the immediate treatment group and deferred treatment group, and 10 patients in the intensive pharmacokinetic cohort. With this sample size, there is 95% or more power to show that the SVR12 rate in patients receiving grazoprevir and elbasvir is higher than the reference SVR12 rate of 45%, at an overall one-sided 0·025 α level, if the true SVR12 rate of grazoprevir and elbasvir is about 65%. A post-hoc descriptive summary of SVR4 (at week 16) in patients receiving placebo in the deferred treatment group is also reported. SVR12 cannot be reported for the deferred treatment group because these patients began active treatment at week 16.

The full analysis set population was used for the analysis of safety data. Tier 1 event rates were compared between immediate treatment and deferred treatment groups: p values and 95% CIs were calculated using the stratified Miettinen and Nurminen method with baseline dialysis status as the strata.[22] Safety events occurring up to 14 days after completion of treatment were captured to ensure the reporting of events that might be related to persistence of study drug. The study is registered at ClinicalTrials.gov, number NCT02092350.

Role of the funding source

Merck Sharp & Dohme Corp contributed to trial management, data collection, statistical analyses, writing, and review of the report. All authors had access to the data, reviewed and approved the final report, and take full responsibility for the veracity of the data and statistical analysis. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

In total, 237 patients were enrolled and 235 received one or more doses of study drug between March 30, 2014, and Nov 28, 2014. Of these, 224 were assigned to the immediate treatment group (n=111) or deferred treatment group (n=113), and an additional 11 patients were assigned to the intensive pharmacokinetic treatment group (figure 1).

Demographic and baseline characteristics were generally balanced between the immediate treatment group, intensive pharmacokinetic, and deferred treatment group populations (table 1). Overall, 179 (76%) of 235 patients were on haemodialysis and 191 (81%) had chronic kidney disease stage 5 at baseline. 80 (34%) patients had diabetes, 96 (41%) had cardiovascular disease, 122 (52%) had HCV genotype 1a infection, 189 (80%) were HCV treatment-naive, and 14 (6%) were cirrhotic.

Of the 122 patients in the immediate treatment and intensive pharmacokinetic population, six were excluded from the modified full analysis set population for reasons other than virological failure (death, lost to follow-up, non-compliance, patient withdrawal, and withdrawal by physician due to violent behaviour; figure 1). All six patients had HCV RNA less than 15 IU/mL at time of

	Grazoprevir and elbasvir pharmacokinetic population (n=11)	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)	Total (n=235)
(Continued from previous page)				
Previous renal transplant				
Yes	2 (18·2%)	15 (13·5%)	28 (24·8%)	45 (19·1%)
No	9 (81·8%)	96 (86·5%)	85 (75·2%)	190 (80·9%)
Primary aetiology of renal disease				
Hypertension	4 (36·4%)	46 (41·4%)	42 (37·2%)	92 (39·1%)
Type 1 diabetes	2 (18·2%)	4 (3·6%)	7 (6·2%)	13 (5·5%)
Type 2 diabetes	2 (18·2%)	19 (17·1%)	25 (22·1%)	46 (19·6%)
Congenital cystic kidney disease	0	4 (3·6%)	1 (0·9%)	5 (2·1%)
Chronic autoimmune glomerulonephritis	0	11 (9·9%)	5 (4·4%)	16 (6·8%)
Pyelonephritis	0	2 (1·8%)	0	2 (0·9%)
Urinary tract obstruction	0	4 (3·6%)	2 (1·8%)	6 (2·6%)
Cryoglobulinaemia	2 (18·2%)	2 (1·8%)	0	4 (1·7%)
Other	1 (9·1%)	19 (17·1%)	31 (27·4%)	51 (21·7%)

Data are n (%) or mean (SD). *IL28B*=interleukin 28B gene. *Other category applies to 30 patients assessed by Fibrotest but could not be considered cirrhotic.

Table 1: **Patient demographics**

	Grazoprevir and elbasvir immediate treatment group and pharmacokinetic population	Grazoprevir and elbasvir deferred treatment group
SVR12 (HCV RNA<LLoQ)		
Modified full analysis set	115/116 (99·1% [95·3–100·0])	..
Full analysis set	115/122 (94·3% [88·5–97·7])	..
On-treatment and follow-up virological response (mFAS, TND)*		
Treatment week 2	51/122 (41·8%)	0/113
Treatment week 4	94/121 (77·7%)	1/113 (0·9%)
Treatment week 12	119/119 (100%)	1/113 (0·9%)
Follow-up week 4	117/118 (99·2%)	1/113 (0·9%)
On-treatment virological response (mFAS<LLoQ)*		
Treatment week 2	81/122 (66·4%)	0/113
Treatment week 4	109/121 (90·1%)	2/113† (1·8%)
Treatment week 12	119/119 (100%)	1/113 (0·9%)
Follow-up week 4	118/118 (100%)	1/113 (0·9%)
Relapse (mFAS)	1/116 (0·9%)	..

Data are n/N (SVR% [95% CI]) or n/N (SVR%). The 95% CI was estimated based on the Clopper-Pearson method. SVR=sustained virological response. HCV=hepatitis C virus. LLoQ=lower limit of quantification (HCV RNA is detected but <15 IU/mL). mFAS=modified full analysis set. TND=HCV RNA target not detected (no calculated HCV RNA result obtained (ie, HCV RNA undetectable). *Modified full analysis set was not defined for the deferred treatment group so data are presented for the full analysis set population (all patients who received one or more doses of study drug). †In the deferred treatment group, two patients had HCV RNA <LLoQ at treatment week 4; one patient had undetectable HCV RNA and one patient had detectable but unquantifiable HCV RNA.

Table 2: **Virological response**

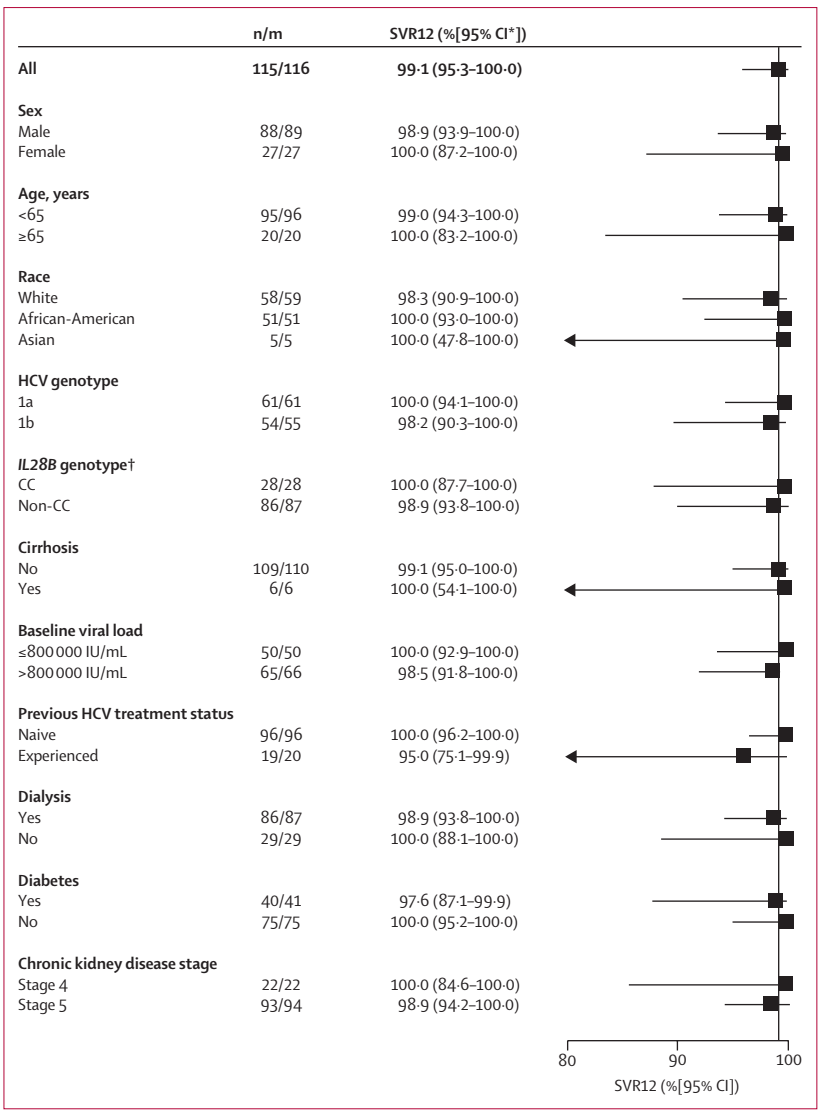

Figure 2: **SVR12 subgroup analyses (modified full analysis set)**
SVR=sustained virological response. m=number of patients included in the analysis. n=number of patients who achieved SVR12 (HCV RNA <LLoQ [<15 IU/mL]) at 12 weeks after end of treatment. *Based on the Clopper-Pearson method. †One patient was missing baseline *IL28B* genotype.

discontinuation. Of the 116 remaining patients (immediate treatment group, n=105; intensive pharmacokinetic group, n=11), 115 (99%) achieved SVR12, a rate better than the historical control rate of 45% (p<0·001). One non-cirrhotic patient with HCV genotype 1b infection and chronic kidney disease stage 5 relapsed 12 weeks after the end of treatment (table 2).

In the full analysis set population, 115 (94%) of 122 patients achieved SVR12. Of the seven patients who did not achieve SVR12, six patients discontinued the study for reasons other than virological failure and one patient relapsed.

High response rates were observed in all subgroups (figure 2), including haemodialysis and non-haemodialysis, and those with characteristics historically associated with poor response to HCV therapy. In particular, SVR12 was achieved in 51 (100%) of 51 African American patients, 86 (99%) of 87 patients with the *IL28B* non-CC genotype, 40 (98%) of 41 patients with diabetes, and all six patients with cirrhosis.

The SVR4 rate in patients receiving placebo in the deferred treatment group was one (<1%) of 113. HCV RNA was undetectable in one patient receiving placebo 4 weeks after the end of the placebo treatment period. This patient denied taking any HCV therapy outside the study, had not initiated deferred active therapy, and it was confirmed that the study drug dispensed during the treatment period was placebo.

Baseline NS3/4A or NS5A resistance-associated variants were detected in 36 (32·1%) of 112 and 17 (14·8%) of 115 patients in the immediate treatment group and intensive pharmacokinetic population with sequencing data, respectively (based on population sequencing). SVR12 was achieved in 36 (100%) of 36 and 16 (94·1%) of 17 of these patients, respectively. The patient who relapsed had an NS5A *L31M* mutation at baseline.

The frequencies of adverse events were comparable between the immediate treatment and deferred treatment groups (76% *vs* 84%; table 3), and most adverse events were of mild or moderate intensity in both treatment groups. The most common adverse events (≥10% frequency) were headache, nausea, and fatigue and were comparable in the two groups. Cardiac serious adverse events were reported in two patients in the immediate treatment group (one cardiac arrest, one myocardial infarction) and three in the deferred treatment group (two myocardial infarctions, one cardiomyopathy; appendix). Two cases of congestive heart failure occurred in the immediate treatment group within 14 days of the end of treatment; one of these, judged by the investigator to be drug-related, was reported 6 weeks after study treatment ended. A total of 16 (14%) patients in the immediate treatment group and 19 (17%) patients in the deferred treatment group reported a serious adverse event during treatment or within 14 days after the end of treatment (appendix). The serious adverse events reported were consistent with the underlying comorbidities and complications within this patient population. The only serious adverse events reported in more than one patient in the immediate treatment group were hypertension and pneumonia (n=2 each). There were no serious adverse events considered to be drug-related in the immediate treatment group.

In the deferred treatment group, serious adverse events reported in more than one patient were upper gastrointestinal haemorrhage (n=2), myocardial infarction (n=2), and aortic aneurysm (n=2). Increased lipase was the only serious drug-related adverse event in the deferred treatment group.

There were no discontinuations due to an adverse event in the immediate treatment group versus five patients in the deferred treatment group (one each

of abdominal pain, elevated ALT and AST, atrial fibrillation with myocardial infarction, increased lipase, and acute myocardial infarction). There were four deaths, none considered related to study drug, during the initial treatment plus 14 day period. One (1%) patient in the immediate treatment group died from cardiac arrest and three (3%) in the deferred treatment group died from aortic aneurysm, pneumonia, and unknown cause of death.

The frequencies and severities of liver function measures were comparable between the immediate treatment and deferred treatment groups (table 3). Rises in ALT and AST were more common among patients receiving placebo than grazoprevir and elbasvir. Rises in bilirubin and alkaline phosphatase and change in blood urea nitrogen from baseline were comparable in both treatment groups (appendix). A higher frequency of low haemoglobin (8·5–<10·0 g/dL) was noted in the immediate treatment group (n=27, 24·3%) than in the deferred treatment group (n=19, 16·8%). Erythropoietin stimulating agents were used during the treatment period by 27 (24%) patients in the immediate treatment group and 34 (30%) patients in the deferred treatment group. No adverse events suggestive of liver decompensation were reported.

The frequencies of renal system adverse events were generally comparable between treatment groups (appendix). Two patients in the immediate treatment group initiated maintenance dialysis during the study and six patients (immediate treatment group, n=4; deferred treatment group, n=2) not on dialysis at baseline had a change in chronic kidney disease stage, based on a decrease in eGFR from 15–29 mL/min per 1·73m² at baseline to less than 15 mL/min per 1·73m². Worsening of proteinuria was reported in four patients in the immediate treatment group (dialysis, n=1; no dialysis, n=3) and eight patients in the deferred treatment group (dialysis, n=4; no dialysis, n=4). There was no consistent change in mean eGFR or creatinine in either treatment group (appendix).

	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)
Any adverse event*†	84 (75·7%)	95 (84·1%)
Headache	19 (17·1%)	19 (16·8%)
Nausea	17 (15·3%)	18 (15·9%)
Fatigue	11 (9·9%)	17 (15·0%)
Insomnia	7 (6·3%)	12 (10·6%)
Dizziness	6 (5·4%)	18 (15·9%)
Diarrhoea	6 (5·4%)	15 (13·3%)
Drug-related adverse event†	38 (34·2%)	39 (34·5%)
Serious adverse event†	16 (14·4%)	19 (16·8%)
Drug-related serious adverse event†	0	1 (0·9%)
Discontinuation due to an adverse event	0	5‡ (4·4%)
Deaths	1 (0·8%)	3 (2·7%)
Lowest haemoglobin on treatment§		
8·5–10·0 g/dL	27 (24·3%)	19 (16·8%)
<8·5 g/dL	5 (4·5%)	5 (4·4%)
Alanine aminotransferase§		
1·1–2·5 × baseline	2 (1·8%)	36 (31·9%)
>2·5 × baseline	1 (0·8%)	6 (5·3%)
>5·0 × baseline	0	1 (0·9%)
Aspartate aminotransferase§		
1·1–2·5 × baseline	4 (3·6%)	38 (33·6%)
>2·5 × baseline	0	4 (4·6%)
>5·0 × baseline	0	0
Bilirubin§		
>2·5–5·0 × baseline	1 (0·9%)	3 (2·7%)
>5·0–10·0 × baseline	0	0
>10·0 × baseline	0	0
Alkaline phosphatase§		
1·1–2·5 × baseline	42 (37·8%)	36 (31·9%)
>2·5 × baseline	0	0
>5·0 × baseline	0	0
Creatinine§ >2·5 × baseline	1 (1·2%)	0
Change in blood urea nitrogen (mg/L) from baseline at treatment week 12§¶	−1·5 (3·6)	0·9 (2·6)

Data are n (%) or mean (SE). *Incidence 10% or more in one or more treatment groups during the initial treatment period and for 14 days after the completion of treatment (all patients as treated). †Number of patients with the specific adverse event. ‡Abdominal pain, elevated alanine transaminase and aspartate transaminase, acute myocardial infarction, atrial fibrillation with myocardial infarction, and increased lipase. §Data presented for patients with more than 1·0 change from baseline. ¶Patients not on dialysis at baseline (immediate treatment group, n=25; deferred treatment group, n=24).

Table 3: **Safety and adverse events (initial treatment period and first 14 days after completion of treatment)**

Discussion

This study shows that the combination of grazoprevir and elbasvir for 12 weeks is an effective treatment regimen for patients with HCV genotype 1 infection and advanced stage 4–5 chronic kidney disease, including patients on haemodialysis and those considered difficult to treat with interferon-based antiviral therapy. Only one (<1%) of 116 patients who completed treatment with grazoprevir and elbasvir did not achieve SVR12. This non-cirrhotic patient with a NS5A *L31M* mutation at baseline relapsed after having undetectable HCV RNA at the end of treatment and at the 4-week post-treatment visit. No patient had on-treatment virological breakthrough. The short, 12-week duration of treatment with grazoprevir and elbasvir might allow waitlisting of patients for kidney transplant while on treatment for HCV infection, a practice that was previously difficult due to the 24–48 weeks of treatment needed with peginterferon and ribavirin regimens.

The deferred treatment group was used to provide a comparator for safety data collected in the immediate treatment group, given the substantial comorbidities seen in patients with stage 4–5 chronic kidney disease. The safety profiles of patients who received grazoprevir and elbasvir and placebo treatment were comparable, with similar frequencies of adverse events, serious adverse events, and renal and hepatic laboratory

abnormalities. No patient discontinued due to an adverse event in the immediate treatment group. Previous studies of first-generation HCV protease inhibitors have shown a reversible decline in eGFR during treatment;[23] however, no such changes were noted in the present study, and no differences in renal function were noted between treatment groups. The five patients with cardiac serious adverse events reflect the known high prevalence of hypertension, diabetes, and cardiovascular disease in patients with chronic kidney disease, especially those on haemodialysis.

SVR12 response rates in the present study are consistent with those reported in studies of patients with HCV genotype 1 infection and normal renal function. In the C-WORTHY study, a 12-week regimen of grazoprevir and elbasvir resulted in SVR12 in 98% of non-cirrhotic and 97% of cirrhotic patients.[11,12] High response rates with grazoprevir and elbasvir have also recently been reported in patients with HCV infection and normal renal function with previous non-response to first-generation direct-acting antiviral agents and in treatment-naive patients.[13,14] Efficacy in the present study was also generally comparable with that of a 12-week regimen of sofosbuvir plus ledipasvir that achieved an SVR12 rate of 96–99% in non-cirrhotic and 94% in cirrhotic treatment-naive patients with HCV genotype 1 infection and without chronic kidney disease stage 4–5.[24,25]

There are limitations to the present study. Patient numbers in some subgroups were small. Only 14 (6%) cirrhotic patients were included. Also, patients with decompensated liver disease and those receiving peritoneal dialysis were excluded. The results of the C-SURFER study therefore cannot be generalised to all patient subgroups. A recent study including 205 Taiwanese haemodialysis patients with genotype 1b HCV infection reported an SVR rate of 64%.[26] These data suggest that an SVR rate higher than our historical control rate of 45% is achievable in Taiwanese patients with HCV genotype 1b infection on haemodialysis and receiving peginterferon plus ribavirin for 48 weeks. Their result could be an overestimate of the treatment response since their study population was all Asian and thus a high percentage carried the *IL28B* CC genotype which is strongly predictive of SVR. Finally, the present study did not have an active comparator because of the restricted treatment options available for HCV infection in patients with advanced chronic kidney disease.

In conclusion, the results from the C-SURFER study suggest that a once-daily oral regimen of grazoprevir and elbasvir for 12 weeks has an acceptable safety profile and can achieve high rates of SVR in patients with HCV genotype 1 infection and advanced chronic kidney disease. The results of this study show that the efficacy and safety profile of this combination is consistent across many patient subgroups, including those receiving haemodialysis.

Contributors

WG, MR, JW, EB, and SW were responsible for study concept and design. BJ, DR, DRN, AB, AML, MS, HM, PM, SP, M-CL, TH, PJZ, and EZ were responsible for acquisition of data. All authors had responsibility for analysis and interpretation of data. WG, DR, B-YN, and EB did the initial drafting of the manuscript. All authors critically revised the manuscript for important intellectual content. SW did the statistical analysis. All authors did a final review and approved the manuscript.

Declaration of interests

DR has served on advisory boards for Bristol-Myers Squibb and Merck. DRN has received research support from Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, and Merck. AB has served on advisory committees for Merck and Chemocentryx. AML has served on advisory boards for Gilead and Janssen. MS has served on speakers bureau or received grants from Bristol-Myers Squibb, MSD, Gilead, AbbVie, Janssen, and Boehringer. HM has served on speakers bureau and advisory boards for Merck. PM has served on advisory boards for Merck. SP has served as a speaker for GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie; has received grants from Bristol-Myers Squibb, Gilead, Roche, and MSD; and has served as a board member for GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie. M-CL has served as a speaker for Janssen, MSD, Gilead, and Bristol-Myers Squibb, and as a consultant for Janssen and Bristol-Myers Squibb. TH has received research grants from Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Gilead Sciences, Idenix, Ikaria, Janssen, La Jolla Pharmaceuticals, Merck, Mochida, NGM BioPharmaceuticals, Roche, Ocera, Sundise, Salix, Taigen, Takeda, Tobria, Vertex, and Vital Therapies; served as a speaker for Baxter, Bristol-Myers Squibb, Gilead, Janssen, and Salix; and served on advisory boards for Abbvie and Bristol-Myers Squibb. PJZ has received research grants from Merck, Abbvie, and Bristol-Myers Squibb; and served on advisory boards for Abbvie and Janssen. EZ has served on advisory boards for BMS, Abbvie, Merck, Janssen, and Gilead, and as a speaker for Bristol-Myers Squibb, Abbvie, Merck, Janssen, Roche, Novartis, and Gilead. SW, B-YN, MR, EB, JW, and WG are employees and shareholders at Merck.

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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: Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet* 2015; published online Oct 6. http://dx.doi.org/10.1016/S0140-6736(15)00349-9.

Supplementary Materials

Sample Size Considerations

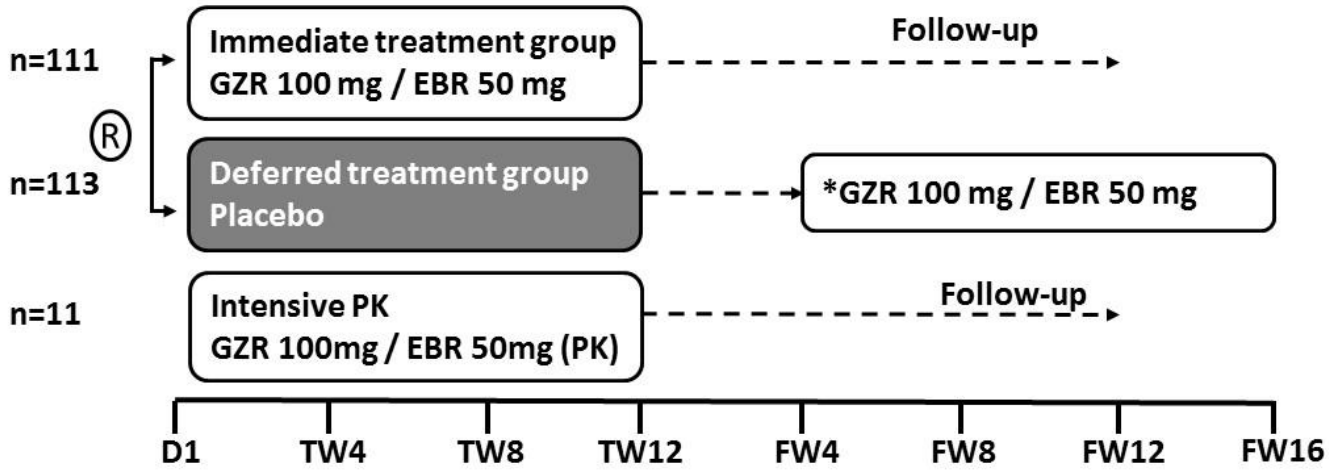
Several considerations led us to choose a reference SVR of 45% for this study:

(1) Interferon (IFN) mono-therapy is recommended for HCV-infected patients with CKD stages 3–5 who are on or not yet on maintenance dialysis therapy. The meta-analyses, conducted by Fabrizi et al, revealed a summary SVR24 of 39% (CI 32–46%).[1]

(2) Given the substantial variation in the G1 proportion of the studies (ranging from 0 to 1) in the Fabrizi meta-analyses, a bayesian logistic regression model for SVR was used to account for the variation of G1 proportions. Twenty studies with G1 proportion were identified from the Fabrizi paper and included in the re-analysis. Non-informative priors were used for the bayesian random-effect model containing a random intercept and a fixed effect of G1 proportion. The model predicts that, if the studies had enrolled 100% G1, the posterior probability/confidence that the true overall population mean for SVR rate would have been at most 45% is about 0.90.

(3) A SVR of approximately 40% was observed in a large study of peginterferon/ribavirin in 3,070 HCV G1-infected patients without renal disease conducted in the United States.[23] The SVR response of patients with CKD stage 4/5 is not expected to be higher than that of the general HCV population without renal disease.

Supplementary Figure 1. Study Design.



*Deferred open-label treatment arm (all randomised patients remained blinded to treatment until FW4).

GZR and EBR were administered as separate entities in the immediate and PK arms, and as a fixed dose-combination in the deferred arm. R = randomised

Supplementary Table 1. Serious adverse events (initial treatment period and first 14 follow-up days; full analysis set)

	Intensive PK arm: GZR 100mg + EBR 50mg for 12 Weeks		**Immediate treatment arm:** GZR 100mg + EBR 50mg for 12 Weeks		**Deferred treatment arm:** GZR Placebo + EBR Placebo for 12 Weeks		**Immediate + Intensive PK arms**: GZR 100mg + EBR 50mg for 12 Weeks	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	11		111		113		122	
with one or more adverse events	0	(0.0)	16	(14.4)	19	(16.8)	16	(13.1)
with no adverse events	11	(100.0)	95	(85.6)	94	(83.2)	106	(86.9)
Cardiac disorders	**0**	**(0.0)**	**2**	**(1.8)**	**3**	**(2.7)**	**2**	**(1.6)**
Acute myocardial infarction	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Angina unstable	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Atrial fibrillation	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Cardiac arrest	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Cardiomyopathy	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Myocardial infarction	0	(0.0)	1	(0.9)	1	(0.9)	1	(0.8)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(1.8)**	**4**	**(3.5)**	**2**	**(1.6)**
Diarrhoea	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Gastritis	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Localised intraabdominal fluid collection	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Pancreatitis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Upper gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	2	(1.8)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**
Death	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**5**	**(4.5)**	**3**	**(2.7)**	**5**	**(4.1)**
Abscess limb	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Appendicitis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Citrobacter sepsis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Enterobacter sepsis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Haematoma infection	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Infected fistula	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Osteomyelitis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Pneumonia	0	(0.0	2	(1.8)	1	(0.9)	2	(1.6)

Injury, poisoning and procedural complications	**0**	**(0.0)**	**1**	**(0.9)**	**2**	**(1.8)**	**1**	**(0.8)**
Arteriovenous fistula aneurysm	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Dialysis related complication	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Postoperative fever	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Procedural pain	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(1.8)**	**0**	**(0.0)**
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Lipase increased	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Metabolism and nutrition disorder	**0**	**(0.0)**	**2**	**(1.8)**	**3**	**(2.7)**	**2**	**(1.6)**
Dehydration	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Fluid overload	0	(0.0)	1	(0.9)	1	(0.9)	1	(0.8)
Hyperglycaemia	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.9)**	**1**	**(0.9)**	**1**	**(0.8)**
Intervertebral disc protrusion	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Myositis	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**	**1**	**(0.8)**
Prostate cancer	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Nervous system disorders	**0**	**(0.0)**	**1**	**(0.9)**	**3**	**(2.7)**	**1**	**(0.8)**
Depressed level of consciousness	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Presyncope	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.9**	**0**	**(0.0)**
Renal failure chronic	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**2**	**(1.8)**	**1**	**(0.9)**	**2**	**(1.6)**
Acute respiratory failure	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Pleural effusion	0	(0.0)	1	(0.9)	1	(0.9)	1	(0.8)
Vascular disorders	**0**	**(0.0)**	**4**	**(3.6)**	**5**	**(4.4)**	**4**	**(3.3)**
Aortic aneurysm	0	(0.0)	0	(0.0)	2	(1.8)	0	(0.0)
Extremity necrosis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)

Hypertension	0	(0.0)	2	(1.8)	1	(0.9)	2	(1.6)
Hypertensive crisis	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.8)
Orthostatic hypotension	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Peripheral venous disease	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

Supplementary Table 2. Liver function tests

Test Name (Unit)	Criterion[†]	Intensive PK arm: GZR 100 mg + EBR 50 mg for 12 Weeks (N=11) n/m	(%)	Immediate treatment arm: GZR 100 mg + EBR 50 mg for 12 Weeks (N=111) n/m	(%)	Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks (N=113) n/m	(%)	Immediate + Intensive PK arms: GZR 100 mg + EBR 50 mg for 12 Weeks (N=122) n/m	(%)
CHEMISTRY									
Alanine aminotransferase (IU/L)	Grade 1: 1·25–2·5× ULN	0/11	(0·0)	3/111	(2·7)	25/113	(22·1)	3/122	(2·5)
Range: 10-33 IU/L (females)	Grade 2: 2·6–5·0× ULN	0/11	(0·0)	1/111	(0·9)	3/113	(2·7)	1/122	(0·8)
10-40 IU/L (males)	Grade 3: 5·1–10·0× ULN	0/11	(0·0)	0/111	(0·0)	2/113	(1·8)	0/122	(0·0)
	Grade 4: >10·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	1·1–2·5× Baseline	0/11	(0·0)	2/111	(1·8)	36/113	(31·9)	2/122	(1·6)
	>2·5–5·0× Baseline	0/11	(0·0)	1/111	(0·9)	6/113	(5·3)	1/122	(0·8)
	>5·0× Baseline	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
Aspartate aminotransferase (IU/L)	Grade 1: 1·25–2·5× ULN	0/11	(0·0)	2/111	(1·8)	21/113	(18·6)	2/122	(1·6)
Range: 10-36 IU/L (females)	Grade 2: 2·6–5·0× ULN	0/11	(0·0)	0/111	(0·0)	2/113	(1·8)	0/122	(0·0)
10-43 IU/L (males)	Grade 3: 5·1–10·0× ULN	0/11	(0·0)	0/111	(0·0)	2/113	(1·8)	0/122	(0·0)
	Grade 4: >10·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	1·1–2·5× Baseline	0/11	(0·0)	4/111	(3·6)	38/113	(33·6)	4/122	(3·3)
	>2·5–5·0× Baseline	0/11	(0·0)	0/111	(0·0)	4/113	(3·5)	0/122	(0·0)
	>5·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)

Bilirubin (mg/dL)	Grade 1: 1·1–1·5× ULN	0/11	(0·0)	1/111	(0·9)	2/113	(1·8)	1/122	(0·8)
Range: 0.10-1.10 mg/dL	Grade 2: 1·6–2·5× ULN	0/11	(0·0)	0/111	(0·0)	2/113	(1·8)	0/122	(0·0)
	Grade 3: 2·6–5·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	Grade 4: >5·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	>2·5–5·0× Baseline	0/11	(0·0)	1/111	(0·9)	3/113	(2·7)	1/122	(0·8)
	>5·0 -10·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	>10·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)

[†]A subject was included in the highest applicable toxicity grade per test as determined by his/her worst post-baseline test result (for the specified study phase(s)) that was also worse than baseline. For tests with additional non-graded criterion categories, a subject was also included in the highest applicable non-graded category as determined by his/her worst post-baseline abnormal test result for the specified study phase(s).

The baseline test result is the result from the latest sample before the start of study therapy.

N=Number of subjects randomly assigned in the treatment group.

n=Number of subjects with test results that met predetermined criteria and were worse than baseline.

m=Number of subjects with a baseline test result and at least one postbaseline result.

LLN=Lower limit of normal range. ULN=Upper limit of normal range.

Supplementary Table 3. Laboratory safety summary

Test Name (Unit)	Criterion[†]	Intensive PK arm: GZR 100 mg + EBR 50 mg for 12 Weeks (N=11) n/m	(%)	Immediate treatment arm: GZR 100 mg + EBR 50 mg for 12 Weeks (N=111) n/m	(%)	Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks (N=113) n/m	(%)	Immediate + Intensive PK arms: GZR 100 mg + EBR 50 mg for 12 Weeks (N=122) n/m	(%)
CHEMISTRY									
Albumin (gm/dL)	Grade 1: 3·0–<LLN	1/11	(9·1)	6/111	(5·4)	8/113	(7·1)	7/122	(5·7)
Range: 3.5-5.5 gm/dL	Grade 2: 2·0–2·9	0/11	(0·0)	3/111	(2·7)	5/113	(4·4)	3/122	(2·5)
	Grade 3: <2·0	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
	Grade 4: Not Applicable	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
Alkaline phosphatase (IU/L)	Grade 1: 1·25–2·5× ULN	0/11	(0·0)	27/111	(24·3)	23/113	(20·4)	27/122	(22·1)
Range: 30-115 IU/L (females)	Grade 2: 2·6–5·0× ULN	0/11	(0·0)	2/111	(1·8)	4/113	(3·5)	2/122	(1·6)
43-115 IU/L (males)	Grade 3: 5·1–10·0× ULN	0/11	(0·0)	0/111	(0·0)	3/113	(2·7)	0/122	(0·0)
	Grade 4: >10·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	1·1–2·5× Baseline	2/11	(18·2)	42/111	(37·8)	36/113	(31·9)	44/122	(36·1)
	>2·5–5·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	>5·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
Amylase (IU/L)	Grade 1: 1·1–1·5× ULN	5/11	(45·5)	29/111	(26·1)	29/113	(25·7)	34/122	(27·9)
Range: 35-121 IU/L	Grade 2: 1·6–2·0× ULN	3/11	(27·3)	21/111	(18·9)	17/113	(15·0)	24/122	(19·7)

	Grade 3: 2·1–5·0× ULN	1/11	(9·1)	24/111	(21·6)	22/113	(19·5)	25/122	(20·5)
	Grade 4: >5·0× ULN	0/11	(0·0)	0/111	(0·0)	4/113	(3·5)	0/122	(0·0)
Creatine kinase (IU/L)	Grade 1: 3·0–5·9× ULN	1/11	(9·1)	6/111	(5·4)	2/113	(1·8)	7/122	(5·7)
Range: 24-169 IU/L (females)	Grade 2: 6·0–9·9× ULN	1/11	(9·1)	1/111	(0·9)	1/113	(0·9)	2/122	(1·6)
24-207 IU/L (males)	Grade 3: 10·0–19·9× ULN	1/11	(9·1)	0/111	(0·0)	1/113	(0·9)	1/122	(0·8)
	Grade 4: ≥20·0× ULN	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
Creatinine (mg/dL)	Grade 1: 1·1–1·3× ULN	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
Range: 0.7-1.4 mg/dL	Grade 2: 1·4–1·8× ULN	0/11	(0·0)	3/111	(2·7)	3/113	(2·7)	3/122	(2·5)
	Grade 3: 1·9–3·4× ULN	4/11	(36·4)	14/111	(12·6)	19/113	(16·8)	18/122	(14·8)
	Grade 4: ≥3·5× ULN	4/11	(36·4)	74/111	(66·7)	76/113	(67·3)	78/122	(63·9)
	>2·5× Baseline	0/11	(0·0)	1/111	(0·9)	0/113	(0·0)	1/122	(0·8)
Direct bilirubin (mg/dL)	Grade 1: 1·1–1·5× ULN	0/11	(0·0)	1/111	(0·9)	3/113	(2·7)	1/122	(0·8)
Range: 0.00-0.40 mg/dL	Grade 2: 1·6–2·5× ULN	0/11	(0·0)	0/111	(0·0)	3/113	(2·7)	0/122	(0·0)
	Grade 3: 2·6–5·0× ULN	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
	Grade 4: >5·0× ULN	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	>2·5–5·0× Baseline	0/11	(0·0)	0/111	(0·0)	2/113	(1·8)	0/122	(0·0)
	>5·0–10·0× Baseline	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
	>10·0× Baseline	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
Gamma glutamyl transferase (IU/L)	Grade 1: 1·1–2·5× ULN	0/11	(0·0)	8/111	(7·2)	33/113	(29·2)	8/122	(6·6)

Range: 5-32 IU/L (females)	Grade 2: 2·6–5·0× ULN	0/11	(0·0)	3/111	(2·7)	8/113	(7·1)	3/122	(2·5)
10-49 IU/L (males)	Grade 3: 5·1–20·0× ULN	0/11	(0·0)	1/111	(0·9)	13/113	(11·5)	1/122	(0·8)
	Grade 4: >20·0× ULN	0/11	(0·0)	0/111	(0·0)	4/113	(3·5)	0/122	(0·0)
Triacylglycerol lipase (IU/L)	Grade 1: 1·1–1·5× ULN	0/11	(0·0)	25/111	(22·5)	17/113	(15·0)	25/122	(20·5)
Range: 13-60 IU/L	Grade 2: 1·6–3·0× ULN	6/11	(54·5)	40/111	(36·0)	41/113	(36·3)	46/122	(37·7)
	Grade 3: 3·1–5·0× ULN	1/11	(9·1)	10/111	(9·0)	15/113	(13·3)	11/122	(9·0)
	Grade 4: >5·0× ULN	0/11	(0·0)	9/111	(8·1)	4/113	(3·5)	9/122	(7·4)
COAGULATION									
Prothrombin intl. normalized ratio	Grade 1: 1·1–1·5× ULN	1/11	(9·1)	16/111	(14·4)	7/113	(6·2)	17/122	(13·9)
Range: 0.9-1.1	Grade 2: 1·6–2·0× ULN	0/11	(0·0)	2/111	(1·8)	1/113	(0·9)	2/122	(1·6)
	Grade 3: 2·1–3·0× ULN	0/11	(0·0)	2/111	(1·8)	2/113	(1·8)	2/122	(1·6)
	Grade 4: >3·0× ULN	0/11	(0·0)	0/111	(0·0)	3/113	(2·7)	0/122	(0·0)
	>1·5× Baseline	0/11	(0·0)	6/111	(5·4)	7/113	(6·2)	6/122	(4·9)
HEMATOLOGY									
Eosinophils/leukocytes (%)	> 5% and baseline <5%	5/11	(45·5)	21/111	(18·9)	20/108	(18·5)	26/122	(21·3)
Range: 0.0-7.0 %	> 5% and baseline ≥5%	0/11	(0·0)	19/111	(17·1)	14/108	(13·0)	19/122	(15·6)
Hemoglobin (g/dL)	Grade 1: 10·0–10·9	2/11	(18·2)	24/111	(21·6)	26/113	(23·0)	26/122	(21·3)
Range: 12.5-17.0 g/dL	Grade 2: 9·0–9·9	3/11	(27·3)	20/111	(18·0)	16/113	(14·2)	23/122	(18·9)

	Grade 3: 7·0–8·9	1/11	(9·1)	11/111	(9·9)	6/113	(5·3)	12/122	(9·8)
	Grade 4: <7·0	0/11	(0·0)	1/111	(0·9)	2/113	(1·8)	1/122	(0·8)
	8·5–<10·0	3/11	(27·3)	27/111	(24·3)	19/113	(16·8)	30/122	(24·6)
	<8·5	1/11	(9·1)	5/111	(4·5)	5/113	(4·4)	6/122	(4·9)
Leukocytes (10^3/µL)	Grade 1: 2·0–2·5	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
Range: 3.5-12.5 x 10^3/µL	Grade 2: 1·5–1·999	0/11	(0·0)	0/111	(0·0)	1/113	(0·9)	0/122	(0·0)
	Grade 3: 1·0–1·499	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
	Grade 4: <1·0	0/11	(0·0)	0/111	(0·0)	0/113	(0·0)	0/122	(0·0)
Lymphocytes (10^3/µL)	Grade 1: 0·60–0·65	0/11	(0·0)	5/111	(4·5)	4/109	(3·7)	5/122	(4·1)
Range: 0.9-3.6 x 10^3/µL	Grade 2: 0·50–0·599	0/11	(0·0)	2/111	(1·8)	4/109	(3·7)	2/122	(1·6)
	Grade 3: 0·35–0·499	0/11	(0·0)	0/111	(0·0)	0/109	(0·0)	0/122	(0·0)
	Grade 4: <0·35	0/11	(0·0)	0/111	(0·0)	0/109	(0·0)	0/122	(0·0)
Neutrophils (10^3/µL)	Grade 1: 1·00–1·3	0/11	(0·0)	1/111	(0·9)	2/109	(1·8)	1/122	(0·8)
Range: 1.7-7.9 x 10^3/µL	Grade 2: 0·75–0·999	0/11	(0·0)	1/111	(0·9)	1/109	(0·9)	1/122	(0·8)
	Grade 3: 0·50–0·749	0/11	(0·0)	0/111	(0·0)	1/109	(0·9)	0/122	(0·0)
	Grade 4: <0·50	0/11	(0·0)	0/111	(0·0)	0/109	(0·0)	0/122	(0·0)
Platelet (10^3/µL)	Grade 1: 100–124·999	2/11	(18·2)	10/110	(9·1)	15/113	(13·3)	12/121	(9·9)
Range: 125-375 x 10^3/µL	Grade 2: 50–99·999	0/11	(0·0)	8/110	(7·3)	12/113	(10·6)	8/121	(6·6)
	Grade 3: 25–49·999	0/11	(0·0)	0/110	(0·0)	0/113	(0·0)	0/121	(0·0)

	Grade 4: <25	0/11 (0·0)	0/110 (0·0)	0/113 (0·0)	0/121 (0·0)

[†]A subject was included in the highest applicable toxicity grade per test as determined by his/her worst post-baseline test result (for the specified study phase(s)) that was also worse than baseline. For tests with additional non-graded criterion categories, a subject was also included in the highest applicable non-graded category as determined by his/her worst post-baseline abnormal test result for the specified study phase(s).

The baseline test result is the result from the latest sample before the start of study therapy.

N=Number of subjects randomly assigned in the treatment group.

n=Number of subjects with test results that met predetermined criteria and were worse than baseline.

m=Number of subjects with a baseline test result and at least one postbaseline result.

LLN=Lower limit of normal range. ULN=Upper limit of normal range.

Supplementary Table 4. Special Renal Function Monitored Adverse Events

	Dialysis status at baseline	Immediate arm: GZR 100 mg + EBR 50 mg for 12 Weeks n (%)	Deferred arm: GZR Placebo + EBR Placebo for 12 Weeks n (%)	Difference in % Immediate – Deferred Estimate (95% CI)[†]
Subjects in population	Overall	111	113	
	On Dialysis	86	87	
	Not On Dialysis	25	26	
Renal function monitor event[‡]	Overall	6 (5·4)	2 (1·8)	3·7 (-1·2, 10·4)
Increasing dialysis frequency	On Dialysis	0 (0·0)	0 (0·0)	0·0 (-4·3, 4·3)
Initiation of maintenance dialysis	Not On Dialysis	2 (8·0)	0 (0·0)	8·0 (-5·6, 25·2)
Increase in CKD stages[§]	Not On Dialysis	4 (16·0)	2 (7·7)	8·3 (-11·1, 28·6)
Number of subjects had baseline and post-baseline urine protein test	Overall	49	50	
	On Dialysis	25	26	
	Not On Dialysis	24	24	
Worsening of proteinuria[‖]	Overall	4 (8·2)	8 (16·0)	-7·9 (-21·8, 5·6)
	On Dialysis	1 (4·0)	4 (15·4)	-11·4 (-30·5, 6·6)
	Not On Dialysis	3 (12·5)	4 (16·7)	-4·2 (-26·0, 17·6)

[†] Based on Miettinen & Nurminen method stratified by dialysis status at baseline; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

[‡] A subject had renal function monitor event if any of the following criteria had occurred from the initiation of study therapy through 14 days following treatment: (1) increasing dialysis frequency in subjects who were on hemodialysis at baseline, (2) initiation of maintenance hemodialysis in subjects who were not on hemodialysis at baseline, or (3) the increase in CKD stages.

[§] For subject who was not on dialysis at baseline and did not initiate maintenance dialysis during the course of the trial, the increase in CKD stages was determined by whether the subject had decrease of eGFR from CKD 4 category (15-29) at baseline to CKD 5 category (<15) during the treatment.

[‖] Elevation of proteinuria is defined as any elevation of protein grade from baseline by 2 grades or more.

Supplementary Table 5. Change from baseline in eGFR (mL/min/1·73m^2) initial treatment period through 4 weeks after end of treatment in patients not on dialysis at baseline (all subjects as treated)

Visit Time Point	Immediate treatment arm: GZR 100 mg + EBR 50 mg for 12 Weeks		Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks		Difference in Change from Baseline (Immediate – Deferred Arm)
	N	Change from Baseline Mean (SD)	N	Change from Baseline Mean (SD)	Estimate (95% CI)
TW1	23	0·04 (2·06)	26	-1·54 (3·22)	1·58 (0·01, 3·16)
TW2	23	0·22 (3·55)	26	-1·31 (3·17)	1·53 (-0·41, 3·46)
TW3	23	-0·04 (4·49)	25	-1·04 (3·02)	1·00 (-1·21, 3·20)
TW4	24	-0·42 (2·21)	23	-1·30 (2·75)	0·89 (-0·57, 2·35)
TW6	25	-0·36 (5·75)	26	-2·08 (3·11)	1·72 (-0·87, 4·30)
TW8	24	0·88 (4·85)	25	-1·52 (3·28)	2·40 (0·02, 4·77)
TW10	25	-0·24 (4·88)	25	-0·80 (3·15)	0·56 (-1·77, 2·89)
TW12	25	-0·32 (4·65)	24	-1·08 (3·83)	0·76 (-1·69, 3·22)
FW4	24	-0·13 (4·79)	24	-1·13 (4·85)	1·00 (-1·80, 3·80)

Supplementary Table 6. Change from baseline in serum creatinine (mg/dL) initial treatment period through 4 weeks after end of treatment in subjects not on dialysis at baseline (all subjects as treated)

Visit Time Point	Immediate treatment arm: GZR 100 mg + EBR 50 mg for 12 Weeks		Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks		Difference in Change from Baseline (Immediate – Deferred Arm)
	N	Change from Baseline Mean (SD)	N	Change from Baseline Mean (SD)	Estimate (95% CI)
TW1	23	0·02 (0·31)	26	0·12 (0·31)	-0·09 (-0·27, 0·08)
TW2	23	-0·04 (0·45)	26	0·05 (0·33)	-0·10 (-0·32, 0·13)
TW3	23	0·03 (0·58)	25	0·05 (0·36)	-0·03 (-0·31, 0·25)
TW4	24	0·05 (0·59)	23	0·10 (0·37)	-0·05 (-0·34, 0·24)
TW6	25	0·24 (1·09)	26	0·17 (0·37)	0·07 (-0·39, 0·52)
TW8	24	-0·19 (0·62)	25	0·10 (0·33)	-0·28 (-0·57, -0·00)
TW10	25	0·04 (0·85)	25	0·09 (0·34)	-0·04 (-0·41, 0·33)
TW12	25	0·07 (0·96)	24	0·13 (0·35)	-0·06 (-0·48, 0·36)
FW4	24	0·00 (1·01)	24	0·18 (0·46)	-0·18 (-0·64, 0·28)
N = Number of patients with results at baseline and the analysis time point.					

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TITLE:

A Phase II/III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 and MK-8742 in Subjects with Chronic Hepatitis C Virus Infection and Chronic Kidney Disease

IND NUMBER: [110,261]
EudraCT NUMBER: [2013-003858-25]

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
5.1.2	Subject Inclusion Criteria	Updated patient population in inclusion criteria #3 and #4 t

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
2.1	Trial Design	Updated study population
4.1.3	Ongoing Clinical Trials	Updated PN 035 Part B study cirrhotic results
4.2.1	Rationale for The Trial and Selected Study Population	Updated study population
5.1.2	Subject Inclusion Criteria	Updated patient population in inclusion criteria #3 and #4
5.1.3	Subject Exclusion Criteria	Updated laboratory exclusion values table for platelet criteria
7.2.3.2	Events of Clinical Interest	Added a caveat to definitions of lab ECIs for them to occur while on study therapy and not associated with virological failure

8.2.4.1	Efficacy analysis populations	Clarify the definition of analysis population and treatment group assignment
8.2.8	Subgroup Analyses and Effects of Baseline Factors	The section was modified with respect to the changes of study inclusion criteria
8.2.10	Compliance (Medical Adherence)	Added the section
11.0	List of References	Added 1 new reference

1.0 TRIAL SUMMARY

Abbreviated Title	MK-5172 in Combination with MK-8742 in subjects with HCV and Chronic Kidney Disease
Trial Phase	Phase II/III
Clinical Indication	Treatment of hepatitis C virus infection
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	**Immediate Treatment**: MK-5172 100 mg + MK-8742 50 mg for 12 weeks **Deferred Treatment**: MK-5172 placebo+ MK-8742 placebo for 12 weeks + 4 weeks unblinding period follow-up followed by MK-5172 100 mg + MK-8742 50 mg for 12 weeks **Intensive PK**: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (open-label)
Number of trial subjects	Approximately 220 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 3 months of enrollment (12 weeks) + up to 60 days of screening (8.5 weeks) + up to 24 weeks of treatment (active or placebo/active) + 4 week unblinding period (deferred treatment arm only) + 24 weeks of follow-up for a total of 72.5 weeks from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 44.5 or 60.5 weeks (depending on the treatment arm) from the time the subject signs the Informed Consent Form (ICF) through the final contact depending on randomization. After a screening phase of 60 days, each subject will be receiving assigned treatment for approximately 12 or 24 weeks. After the end of treatment each subject will be followed for 24 weeks (deferred treatment arm will be followed for an additional 4 weeks post-placebo treatment).

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, parallel-group, multi-site, placebo controlled trial of MK-5172 and MK-8742 in subjects with Hepatitis C and Chronic Kidney disease (CKD) to be conducted in conformance with Good Clinical Practices.

The trial will enroll approximately 220 cirrhotic and non-cirrhotic, Genotype 1 (GT1), HCV patients who have chronic kidney disease (CKD). A definition of the HCV and CKD disease status for targeted subjects in this study is included in Table 1. Patients on maintenance

hemodialysis (including subjects awaiting renal transplant and subjects with a previous failed kidney transplant no longer on immunosuppressant therapy) and patients with CKD stages 4-5 who are not on hemodialysis will be enrolled with a minimum of 20% of patients in the latter category. Subjects must be either treatment naïve to all HCV treatments including any direct acting antivirals (DAA) or are intolerant or who have relapsed or were null-responders to a prior IFN-based treatment regimen. Subjects are required to undergo liver biopsy or non-invasive test to determine the presence or absence of cirrhosis.

Study subjects (210) will be randomized in a 1:1 ratio to receive MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed (immediate treatment group) or 12 weeks of placebo to MK-5172 and MK-8742 followed by unblinding (after a 4 week unblinding period) and then 12 weeks of MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed (deferred treatment group).

In addition, 10 subjects (5 on hemodialysis and 5 non-dialysis CKD) will be assigned to receive open-label MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed. These 10 subjects will constitute the Intensive PK arm.

Table 1 Definition of HCV and CKD in Target Subject Population

Hepatitis C Disease Status
Chronic HCV Genotype 1 infection
With or without evidence of cirrhosis **Cirrhosis is defined as any one the following [44,41]:** • 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 >12.5kPa [41]* • A FibroSure® (Fibrotest®) performed during screening with a score of >0.75 **and** an Aspartate Aminotransferase to Platelet Ratio Index (APRI) of >2.
Treatment naive to l anti-HCV treatment including any DAA OR Prior Treatment Relapsers: Subjects that have relapsed after completing a prior course of HCV therapy that included interferon (IFN or PEG-IFN ± Ribavirin) but that did not include any licensed or investigational direct acting antiviral agents (DAAs) OR P/R Partial responder: > 2 log10 IU/mL reduction in HCV RNA by week 12 of treatment, but HCV RNA quantifiable (≥ LLOQ) at the end of treatment. OR Null Responder: Subjects had a <2 log10 IU/mL reduction in HCV RNA at Week 12 OR <1 log10 IU/mL decline from baseline at Week 4 while on a prior course of HCV therapy that included IFN or PEG-IFN ± Ribavirin but that did not include any direct acting antivirals and discontinued therapy prior to Week 12 OR Subjects who prematurely discontinued an IFN or PEG-IFN regimen± Ribavirin (that did not include any licensed or investigational DAAs) because of drug intolerance.
Chronic Kidney Disease Status
CKD Stages 4-5: Subjects with eGFR (by the MDRD-4) ≤29 ml/min/1.73m^2 who are not on dialysis OR CKD-5D: Subjects on hemodialysis (including subjects awaiting renal transplantation)

Administration of a 12 week regimen of MK-5172+MK-8742 regimen (without ribavirin) to treatment-naïve and treatment-experienced, cirrhotic and non-cirrhotic GT1 patients was highly efficacious in an ongoing PN035 trial (see Section 4.1.3).

Safety and tolerability will be carefully monitored throughout the study by the SPONSOR (or designee) in accordance with standard procedures and also by an external Data Monitoring Committee (eDMC).

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

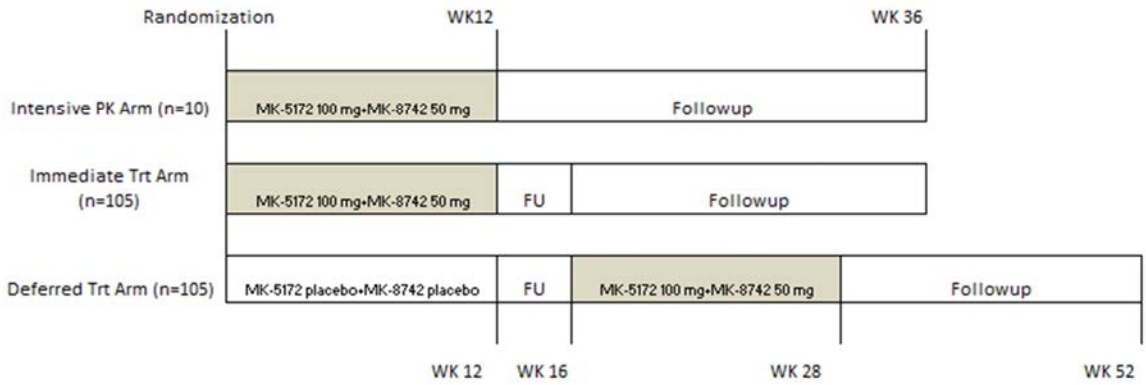

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects who have chronic kidney disease (CKD Stages 4-5) and 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 MK-5172 + MK-8742 in HCV GT1 subjects with chronic kidney disease (CKD) within the immediate treatment and the intensive PK groups.

Hypothesis: The proportion of HCV GT1 infected CKD 4-5 subjects achieving SVR (defined as HCV RNA <LLoQ (either TD(u) or TND) 12 weeks after the end of all study therapy will be superior to 45% (see Section 4.2.1- Rationale for Study).

(2) **Objective:** To evaluate the safety and tolerability of MK-5172 in combination with MK-8742 in the immediate treatment group relative to the placebo treatment of the deferred treatment group.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving:

- SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy) within the immediate treatment and the intensive PK groups, defined as HCV RNA <LLoQ (either TD(u) or TND) 24 weeks after the end of all study therapy.

- SVR_4 (Sustained Virologic Response 4 weeks after the end of all study therapy), defined as HCV RNA <LLoQ (either TD(u) or TND) 4 weeks after the end of all study therapy.

- SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA <LLoQ (either TD(u) or TND) 12 weeks after the end of all study therapy on active period of deferred treatment arm,

- SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA <LLoQ (either TD(u) or TND) 12 weeks after the end of all study therapy for all active treatment arms combined.

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

(3) **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.

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

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

(2) **Objective:** To evaluate the pharmacokinetic/pharmacodynamics (PK/PD) relationship of MK-5172 and MK-8742 plasma levels to efficacy and safety.

(3) **Objective:** To evaluate biomarkers (e.g., proteins and metabolite production), that may be predictive of tolerability of study drugs and virologic response to MK-5172 in combination with MK-8742 by comparing biomarker levels over time in subjects who respond or fail study therapy.

(4) **Objective:** To describe and compare changes from baseline in health-related quality of life during and after active and placebo treatment periods.

(5) **Objective:** To assess the genetic variation in the human IL28B gene as a predictor of virologic response in each treatment arm.

(6) **Objective:** To determine the impact of HCV treatment on cryoglobulinemia in the patients with CKD.

4.0 BACKGROUND & RATIONALE

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5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with GT1 HCV who are cirrhotic or noncirrhotic and also have Chronic Kidney Disease who are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be ≥18 years of age on day of signing informed consent.

2. Have documented chronic (at least 6 months) HCV GT1 infection (with no evidence of non typable or mixed genotypes) :

   - Positive for anti-HCV antibody, HCV RNA, or an HCV genotype
   - HCV RNA (≥ 10,000 IU/mL in peripheral blood)

3. Subjects with or without cirrhosis may be enrolled into this study. All subjects must have one of the below liver disease staging assessments as follows:

   - Liver biopsy performed within 24 months of Day 1 (if subject is cirrhotic then there is no time restriction on biopsy)

- Fibroscan performed within 12 months of Day 1
- A FibroSure® (Fibrotest®) **and** Aspartate Aminotransferase to Platelet Ratio Index (APRI) (APRI is automatically calculated by central laboratory) during Screening

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above critieria, a liver biopsy is required. Liver biopsy results supersede the results obtained by Fibroscan or FibroSure®.

4. Have an HCV treatment status that is one of the following:

   Treatment naïve: Naive to all anti-HCV treatment

   Prior IFN or PEG-IFN ± Ribavirin Treatment failures: Null responders, Partial responders, Relapsers

   P/R Intolerant: Subjects were intolerant to a prior IFN or PEG-IFN ± Ribavirin regimen, Subjects discontinued treatment prematurely and were therefore unable to complete a full course of therapy because of drug-related toxicity.

5. Have Chronic Kidney Disease defined as:

   Subjects with GFR ≤29 who are non-dialysis dependent (NDD) or have been on hemodialysis (HD) for at least 3 months (including subjects awaiting kidney transplant and subjects with failed kidney transplants no longer on immunosuppressant therapy).

6. Agree (if subject is of reproductive potential) to remain truly abstinent or use (or have their partner use) 2 acceptable methods of birth control from at least 2 weeks prior to Day 1 through 14 days after the last dose of study drugs, or longer if dictated by local regulations.

   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 or vasectomy.

   Note: Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal methods, use of post-ovulation methods and withdrawal) are not acceptable methods of contraception.

7. A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subjects who is not of reproductive potentials 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.

8. 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.

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

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

5.1.3 Subject Exclusion Criteria

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

1. Is under the age of legal consent, is mentally or legally incapacitated, has significant emotional problems at the time of pre-study screening visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder which, in the opinion of the investigator, would interfere with the study procedures.

2. Evidence of decompensated liver disease manifested by the presence of or history of ascites, gastric or variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver disease.

3. Is on peritoneal dialysis for management of Kidney disease

4. In the opinion of the investigator the subject has a high likelihood of receiving a renal transplant during the study treatment period (up to 24 weeks from Day 1).

5. Is coinfected with hepatitis B virus (e.g. HBsAg positive) or HIV.

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

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 such study during the course of this study.

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

  NOTE: Subjects receiving opiate agonist substitution therapy are not excluded from the study if, in the opinion of the investigator, the subject is capable of complying with all study procedures

- history of 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. Female subject who is pregnant or breast-feeding, or expecting to conceive or donate eggs from Day 1 through 14 days after the last dose of study drugs, or longer if dictated by local regulations or male subject who is expecting to donate sperm from Day 1 through 14 days after the last dose of study drugs, or longer if dictated by local regulations.

11. Has any of the following conditions:

    - Organ transplants (including hematopoietic stem cell transplants) other than kidney, cornea and hair.

    - Poor venous access in non-dialysis patients that precludes routine peripheral blood sampling required for this trial.

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

    - Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the trial.

    - Has uncontrolled or poorly controlled hypertension including but not limited to hypertensive emergency or hospitalization for hypertension in preceding 3 months.

    - Diagnosed with a significant cardiovascular disorder (e.g. MI or unstable angina) or has had a cardiovascular procedure (e.g. CABG or PTCA) within 3 months prior to signing informed consent.

    - Has new or worsening signs or symptoms of congestive heart failure within 3 months of signing informed consent.

- Has severe active peripheral vascular disease, (e.g., manifested by claudication with minimal activity, a non-healing ischemic ulcer, or disease which is likely to require intervention such as with bypass or angioplasty).

- Has a recent (within 3 months prior to signing informed consent) diagnosis, episode or recurrence of stroke, TIA or neurological disorder, including but not limited to seizures, blackouts, or a recent (within 3 months prior to signing informed consent) change in the dose or class of medications used to treat these conditions.

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

13. Had a life-threatening SAE during the screening period.

14. 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.

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

16. Has exclusionary laboratory values as listed below (Table 4):

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

Table 4 Laboratory Exclusionary Values

Laboratory Assessment	Exclusionary Value
eGFR	>29 mL/min
hemoglobin	< 9.0 g/dL
neutrophils	<1.5 x 10^3/µL (<1.2 x 10^3/µL for Blacks)
platelets	<70 x 10^3/µL
direct bilirubin	>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)
Serum Albumin	< 3.0 g/dL (lower limit of normal) of laboratory reference range
INR	>1.7, unless subject has a stable INR on an anticoagulant regimen
ALT	>350
AST	>350

17. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatment

Drug	Weight	Dose/Potency	Dose Frequency	Route of Administra-tion	Regimen/Treatment Period	Use
MK-5172	N/A	100 mg	QD	Oral	12 Weeks	experimental
MK-8742	N/A	50 mg	QD	Oral	12 Weeks	experimental
MK-5172 Placebo	N/A	0	QD	Oral	12 Weeks	experimental
MK-8742 Placebo	N/A	0	QD	Oral	12 Weeks	experimental

The first dose of trial treatment will be taken by the subject in the evening of Day 1 (Visit 2) for all subjects (Immediate Treatment, Deferred Treatment and Intensive PK arms) and in the evening of the Week 16 visit (Visit 10) only for subjects in the deferred treatment arm. Subsequent dosing will be taken in the evenings by the subject at approximately the same time each day (except for Week 12 and Week 28 doses which must be withheld the night before for the predose PK collection at those visits).

The single entity tablet formulations will be used in the Intensive PK arm and for the first 12 weeks of dosing in the Immediate Treatment and Deferred Treatment arms. The fixed dose combination formulation will be used for Week 16 to Week 28 dosing in the Deferred Treatment arm.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

5.2.1.2 Dose Modification (Escalation/Titration/Other)

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

5.2.2 Timing of Dose Administration

Subjects will be instructed to take MK-5172 and MK-8742 together at bedtime. Phosphate binders should be taken at least 3 hours before or at least 3 hours after taking the investigational study medications.

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. Subjects should not double the next dose in order to compensate for what has been missed.

For the Week 12 and 28 (for deferred treatment arm) visits, all subjects will withhold their last evening dose of study medications. Subjects will have a predose sample taken the next morning at their study visit, subjects will then take their study medications, and have a 2 hour post dose sample taken.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-5172 and MK-8742 and placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the [treatment] or clinical evaluation of the subjects are unaware of the group assignments.

The subject, the investigator and the Sponsor will not know the treatment they are administered or the HCV RNA results through Week 12 of the study, including in-house team responsible for medical monitoring. A separate, in-house unblinded team will have access to the treatment group assignments and HCV RNA results. (Please note, the 10 subjects assigned to the intensive PK Arm will be open-label)

Pharmacokinetic (PK) measurements will be conducted in support of PK evaluations. Additionally, a small team as specified in a separate Modeling and Simulation (M&S) Modeling Analysis Plan, and who are separate from the study team, will be unblinded for the purpose of preparing the pharmacokinetic analyses. No PK data or results from the PK analyses will be shared with the study team, and the unblinded group will not be members of the study team.

<u>Unblinding Procedures</u>

A subject will not be unblinded until the Follow-Up Week 4 visit. All safety data through the first 12 weeks of treatment for that subject will be cleaned prior to unblinding, changes to the causality asessments that occurred through Week 12 will not be allowed after the subject is unblinded at Follow-Up Week 4.

See Section 7.1.5.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such an action be warranted.

5.3 Randomization or Treatment Allocation

Treatment Allocation will occur centrally using an interactive voice response system (IVRS). In order to ensure enrollment of at least 20% CKD 4-5 NDD subjects, the site will identify if the subject is HD or NDD at the time of screening. In addition the subject's prior HCV treatment status will be entered into the IVRS system at screening.

5.4 Stratification

Randomization will be stratified according to the following factors:

- Dialysis: Yes/No
- Diabetes: Yes/No

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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

- At each visit, subjects should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

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

Known hepatotoxic drugs, including but not limited to:

- Etofoxine
- Isoniazid
- Nitrofurantoin
- Phenytoin

Herbal supplements

Strong 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
- Lipid lowering agents: gemfibrozil
- eltrombopag
- lapatinib

HIV medications, including but not limited to:

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

HMG-CoA reductase inhibitors (statins), including but not limited to:

- simvastatin
- fluvastatin
- rosuvastatin
- atorvastatin
- pitavastatin
- pravastatin at doses greater than 10 mg
- **Note: Questions regarding use of other statins should be directed to the Sponsor.**

In general, CYP3A4 substrates with narrow therapeutic ranges (e.g. alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, terfenadine) are not

prohibited, but their levels have the potential to be increased by approximately 30%. Therefore, subjects taking these medications should be monitored closely or dose adjusted appropriately.

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.

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

Allowed Medications

The following concomitant medications are allowed in this study:

Phosphate binders such as
- calcium carbonate/calcium acetate
- sevelamer
- lanthanum

Note: Subjects taking phosphate binders must do so either at least 3 hours before or at least 3 hours after taking the investigational study medications.

Statins such as
- pravastatin: use the lowest possible effective dose, but do not exceed a daily dose of 10 mg

Note: Questions regarding use of other statins should be directed to the Sponsor.

Medications for anemia such as
- Erythropoetin

Antihypertensives
- ACE inhibitors/ARBs: enalapril, captopril, lisinopril, ramipril, valsartan, losartan, telmisartan
- Most beta blockers: atenolol, metoprolol, propranolol
  Note: for other beta blockers, please consult with the Sponsor
- calcium-channel blockers: verapamil, diltiazem, amlodipine
  Note: For other antihypertensives, please consult with the Sponsor
- hydralazine, clonidine, minoxidil, isosorbide nitrates

Medications for hyperparathyroidism
- ergocalciferol
- vitamin D analogs: calcitriol, paricalcitol, doxercalciferol, alfacalcidol, falecalcitriol, 22-oxacalcitriol
- calcimimetics: cinacalcet

Diuretics
- HCTZ
- furosemide
- spironolactone
- triamterene

Hypoglycemic agents
- Insulin
- Sitagliptin

Anticoagulants
- Warfarin

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

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

Dietary Considerations

MK-5172 and MK-8742 can be taken without regard to food; however, intake of grapefruit or grapefruit juice is prohibited during the dosing period of the trial.

Subjects taking phosphate binders must do so either 3 hours before or three hours after the investigational study medications administered in this study.

Considerations for Study Visits

Procedures visits should be scheduled as close to the indicated study days and study weeks as possible. See the Study Flow Chart in Section 6 for a complete listing of study procedures required at each visit. Collection of PK samples (predose and/or postdose) must be taken as indicated in Table 7, Table 8, and Table 9 in Section 7.1.4.2

5.8 Subject Withdrawal/Discontinuation Criteria

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

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. 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:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

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

- Subject meets any 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.
- Subject receives a renal transplant.
- 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 >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 and or MK-8742: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).
- The subject's ALT or AST increases to >3x the nadir value, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following adverse events that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to MK-5172 and or MK-8742: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).

- The subject's alkaline phosphatase increases to >3x ULN, there is a simultaneous increase in total bilirubin > 2x ULN and other causes of elevated alkaline phosphatase are excluded.

- The subject's alkaline phosphatase increases to >5x ULN and other causes of elevated alkaline phosphatase are excluded.

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

- SAE assessed by the physician investigator as possibly or probably related to study medication. Investigator may continue the subject in the trial, if it is deemed to be in the best interest of the subject to stay on the study treatment.

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

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last 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 will be the result of the criteria specified below:

Early Trial Termination Due to Safety

If >10 of 115 in the immediate treatment arm or Intensive PK arm meet any of the safety criteria listed below, then the study should be terminated.

- 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 Virologic Failure Criteria (rebound, non-response, breakthrough, relapse):

All Early Trial Termination decisions will be based on the per-protocol population.

If >7 of the first 20 patients in the immediate treatment group meet virologic failure criteria, no additional subjects will be enrolled and the study will be terminated.

6.0 TRIAL FLOW CHART

				Treatment Days/Weeks																Follow-Up Weeks			Unscheduled Visits	
Immediate Treatment Arm											NA	NA	NA	NA	NA	NA	NA	NA	NA					
Intensive PK Arm[*]	Screen	Day 1	Day 7	2	3	4	6	8	10	12										FU4	FU 12	FU 24	Unsched/HCV Viral Fail Conf Visit	Early Discon Visit
Deferred Treatment Arm											16	17	18	19	20	22	24	26	28					
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**	24
Visit Window	-60 days	NA	-6/+7 days	±1 week		-1/+2 week	±2 week			-2/+4 week	±2 week	±1 week			-1/+2 week	±2 week			-2/+4 week	±2 weeks	±4 weeks		NA	
ADMINISTRATIVE PROCEDURES																								
Informed Consent	x																							
Informed Consent for Future Biomedical Research	x																							
Inclusion/Exclusion Criteria	x																							
Subject Identification Card	x																							
Medical History	x																							
Prior and Con-med Review	x	x	x	x	x	x	x	x	x	x	x	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	x				x	x
Unblinding of treatment assignment											X[14]									X[14]				
CLINICAL SAFETY EVALUATIONS																								
Physical Examination[1]	x	x				x				x	x				x					x				x
Weight	x	x								x	x									x				x
Height	x																							
12-Lead ECG	x					x				x	x				x				x	x				x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Subject confirmation of birth control	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[16]			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	x	x	x	x	x

				Treatment Days/Weeks																Follow-Up Weeks			Unscheduled Visits	
Immediate Treatment Arm																								
Intensive PK Arm[*]	Screen	Day 1	Day 7	2	3	4	6	8	10	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	FU4	FU 12	FU 24	Unsched/HCV Viral Fail Conf Visit	Early Discon Visit
Deferred Treatment Arm											16	17	18	19	20	22	24	26	28					
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**	24
Visit Window	-60 days	NA	-6/+7 days	±1 week		-1/+2 week	±2 week			-2/+4 week	±2 week	±1 week			-1/+2 week	±2 week			-2/+4 week	±2 weeks	±4 weeks		NA	
LABORATORY SAFETY EVALUATIONS[13]																								
Coagulation	x	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	x
Urinalysis [3]	x		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Cryoglobulinemia labs[15]		x								x									x		x			
HBA1C (only for subjects with a prior diagnosis of diabetes)	x						x			x						x			x		x			
HBsAg	x																							
HIV screen	x																							
Pregnancy Test (females of child bearing potential only)[4]	x	x								x									x		x	x	x	x
PATIENT REPORTED OUTCOME																								
SF36® Health Survey		x								x									x		X			x
PHARMACOKINETICS																								
MK-5172 (population PK in all subjects)		X								X									X				x	x
MK-8742 (population PK in all subjects)		X								X									X				x	x
MK-5172 (intensive PK Arm only)		X				X				X													x	x
MK-8742 (intensive PK Arm only)		X				X				X													x	x
MK-5172 (evening pre-dose PK cohort only)						X				X													x	x
MK-8742 (evening pre-dose PK cohort only)						X				X													x	x
HCV EVALUATIONS																								
HCV Genotype Determination	x										x													
HCV RNA Level[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X[11]
Plasma for HCV Viral Resistance and Biomarker[5,7]		x																		x	x	x	x	X[11]
Blood (DNA) for genetic analysis[6]		x																						
Blood (DNA) for Future Biomedical Research[7]		x																						

				Treatment Days/Weeks																Follow-Up Weeks			Unscheduled Visits	
Immediate Treatment Arm	Screen	Day 1	Day 7	2	3	4	6	8	10	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	FU4	FU 12	FU 24	Unsched/HCV Viral Fail Conf Visit	Early Discon Visit
Intensive PK Arm*																								
Deferred Treatment Arm											16	17	18	19	20	22	24	26	28					
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**	24
Visit Window	-60 days	NA	-6/+7 days	±1 week		-1/+2 week	±2 week			-2/+4 week	±2 week	±1 week			-1/+2 week	±2 week			-2/+4 week	±2 weeks	±4 weeks		NA	
DRUG ADMINISTRATION																								
MK-5172 or placebo (blinded)[8]		x	x	x	x	x	x	x	x	x[11,12]														
MK-8742 or placebo(blinded)[8]		x	x	x	x	x	x	x	x	x[11,12]														
MK-5172 (open label)[8]										x[11,12]	x	x	x	x	x	x	x	x	X[11,12]					
MK-8742 (open label)[8]										x[11,12]	x	x	x	x	x	x	x	x	x[11,12]					

NOTE: Subjects in the Immediate treatment arm will have Visits 1-10, be unblinded at Week 16, and will then move to Visits 20-22. Subjects in the Deferred treatment arm will have Visits 1-10, be unblinded at Week 16, and will then have visits 11-22.

[*] **Subjects in the Intensive PK arm will have Visits 1-10 and will then move to Visits 20-22.**

[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] Urinalysis will be obtained on all NDD subjects and when feasible on HD subjects.

[4] Female subject who is of childbearing potential. Serum pregnancy tests at screening visit. Routinely use urine pregnancy tests beginning predose on Day 1, however, a serum pregnancy test can be used for patients on hemodialysis who do not produce enough urine for testing.. The urine pregnancy 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] 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 or leftover plasma for HCV viral resistance and biomarker will be stored for future research if the subject consents to participate in the FBR sub-study.

[8] 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.

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

[10] 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.

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

[12] For the Week 12 (Week 28 for deferred treatment arm), all subjects will hold their last evening dose of study medications. Subjects will have predose sample taken the next morning at their study visit.

[13] All laboratory sampling should be performed prior to dialysis on days with a scheduled dialysis session.

[14] Unblinding will occur at Week 16 of the study after all data through Week 12 and safety follow-up after Week 12 have been completed, data cleaned and queries resolved. If the subject is determined to have received active therapy during the first 12 weeks, the visit at Week16 will be the FU 4 visit and those study procedures should be followed. If the subject was determined to have received placebo during the first 12 weeks, the visit at Week 16 will be counted as Visit 11 (Day 1 of active dosing) and those study visits followed. Unblinding is not applicable to the Intensive PK Arm.

[15] Serum cryocrit, C4 complement component, and Rheumatoid factor should be collected for all subjects with cryoglobulinemia reported in their Medical History. Because of stability and shipping issues, these samples should only be collected on a Monday or Tuesday.

[16] Confirmation of birth control is only needed for 14 days past last dose of study drugs.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

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

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

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated 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 the 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.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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.

Patients with a diagnosis of cryoglobulinemia at study entry should be specifically evaluated for signs and symptoms of the disease.

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. Weight and height will also be utilized to assess the patients GFR in order to monitor the renal disease status.

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

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

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 Noninvasive Methods of Cirrhosis Evaluation

FibroScan - This method for assessing liver cirrhosis has gained increasing acceptance. In the US, this methodology is FDA approved and in other countries it is often the preferred method of assessment. Fibroscan results are influenced by a number of confounders including ALT, ascites, and underlying disease. Hepatitis C is one of the best studied and is the disease state with the most reproducible/reliable results. Fibroscan has been evaluated in many liver diseases for the staging of liver fibrosis, and has been demonstrated to be very effective or differentiating cirrhosis (F4) from no cirrhosis (<F4), but it is less capable of differentiating gradations of fibrosis. In a large study by Castera, et al [42], a population of patients with chronic hepatitis C, a cut-off of 12.5 kPa was selected for cirrhotics. At this cut-off, the sensitivity and specificity of the test for cirrhosis were 87% and 91%, respectively and the negative predictive value was 95%. Since this analysis was assessed specifically in patients with chronic hepatitis C, the cut-off value ≤ 12.5 kPa used by Castera was selected to exclude cirrhotics in the current study.

FibroTest + APRI – Various methodologies have been developed in order to improve the sensitivity and specificity of blood tests used to diagnose cirrhosis in patients with chronic hepatitis C infections. One such algorithm, the Sequential Algorithm for Fibrosis Evaluation (SAFE), which uses a combination of Fibrotest and the aspartate aminotransferase-to platelet ratio index (APRI) is very accurate for diagnosing cirrhosis [43]. For cirrhosis, the SAFE for F4 algorithm provides a diagnostic accuracy of 89.5% with a negative predictive value of 94.6%. Using this algorithm, it is estimated that only 6.2% of the patients would need a liver biopsy to confirm the diagnosis of cirrhosis. The cut-off values for excluding cirrhotics using the two tests, without the use of liver biopsy, are ≤1 and ≤0.48 for FibroTest and APRI when the SAFE for F4 is used. This study uses this method with one variation and that is the more stringent requirement that both the APRI and FibroTest need to be consistent with no cirrhosis, i.e. APRI is ≤1 AND Fibrotest ≤0.48. Accordingly, the Sponsor is confident these cut-off values that will differentiate cirrhotic from non-cirrhotic patients with reasonable accuracy in this study.

7.1.3 Patient-Reported Outcomes

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-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 will be administered the SF-36v2® on an electronic device and are to complete the SF-36v2® on their own at the beginning of the appropriate study visit [Day 1, Week 12, Week 28 (deferred treatment arm only), Follow-Up Week 12, and Early Discontinuation].

Every attempt should be made to complete the questionnaires prior to receiving study treatment, discussing any medical conditions, or receiving any medical results (see study flow chart). 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 12.4.

NOTE: All laboratory sampling should be performed prior to dialysis on days with a scheduled dialysis session.

7.1.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

NOTE: For subjects on hemodialysis, samples should be drawn prior to any scheduled HD.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Specific Gravity	Hemoglobin A1C (HbA1c)
Hemoglobin	Alkaline phosphatase	pH	Hepatitis C Virus Genotype
Platelet count	Alanine aminotransferase (ALT)	Glucose	Plasma HCV RNA
WBC (total and differential)	Aspartate aminotransferase (AST)	Protein	Prothrombin time (PT)
Erythrocytes (RBC count)	Creatinine	Ketones	International normalized Ratio (INR)
	Creatinine Clearance (for CKD patients throughout)	Occult Blood	Human Chorionic gonadotropin (Urine pregnancy test kits to sites)
	Creatine Kinase	Bilirubin	HIV-1 serology (screening only)
	Gamma-glutamyltransferase	Nitrite	HBsAg (screening only)
	Glucose (serum glucose)	Leukocytes	APRI calculation (screening only)
	Potassium	Erythrocytes	Fibrosure® (Fibrotest) as requested by site for entry critiera (may be performed locally)
	Sodium	Microscopic exam, if abnormal results are noted	eGFR calculation
	Total Bilirubin		
	Direct Bilirubin		For subjects with cryoglobulinemia at study entry: • Serum cryocrit (cryoglobulin level)
	Indirect Bilirubin		• Rheumatoid factor
	Total protein		• C4 Complement component
	Blood Urea Nitrogen		
	Amylase		
	Lipase		

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 Quantitative Pharmacology and Pharmacometrics (QPP) and the appropriate department within Late-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 Plasma MK-5172 and MK-8742

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

All subjects allocated and enrolled in the study (all 3 treatment arms) will be part of the population PK group (i.e. sparse PK sampling scheme). See Table 7 for sampling scheme. For the Week 12 sampling, all subjects will withhold their last evening dose of study medications. Subjects will have a predose sample taken the next morning at their study visit, subjects will then take their study medications, and have a 2 hour post dose sample taken. For the Week 28 sampling, subjects in the deferred treatment arm will hold their last evening dose of study medications. Subjects will have a predose sample taken the next morning at their study visit, subjects will then take their study medications, and have a 2 hour post dose sample taken.

Five (5) HD subjects and five (5) subjects not on HD will be allocated to an intensive PK subgroup receiving open-label MK-5172 in combination with MK-8742. See Table 8 for sampling scheme. At Week 4, these 10 subjects will take their study medications in the PM and be domiciled overnight for the sample collections. The 24-hour PK collection in HD and non-HD subjects (Week 4) will be used to characterize the representative steady-state exposures in both populations.

An additional ten (10) HD subjects and ten (10) non-dialysis subjects will be identified from the immediate and deferred treatment arms to participate in an evening pre-dose PK cohort, but only the samples from the subjects on active treatment (immediate treatment arm) will be analyzed. See Table 9 for sampling scheme. A visiting nurse will collect a pre-dose sample at the protocol specified Week 4 PK timepoint prior to their PM dose. The predose PK sample collected in the evening pre-dose PK cohort will be used to correlate the PK exposures between PK samples collected in the AM (e.g., Week 12, 28) and the PM (e.g., Week 4).

All PK samples (from population PK, intensive PK, and evening pre-dose PK) will be used to evaluate not only PK exposures in the non-dialysis CKD and HD populations, but also to assess the PK/PD and PK/AE relationships of MK-5172 and MK-8742, as appropriate.

Table 7 Pharmacokinetic Sampling Timepoints- Population PK (All Subjects)

Visit Number	Study Population	Study Day/Week	Time Relative to Dose of MK-5172, MK-8742[2]	MK-5172 PK Sample[1]	MK-8742 PK Sample[1]
2	All 3 treatment arms	Day 1	Predose	x	x
10	All 3 treatment arms	Week 12	Predose	x	x
			~2 hrs Postdose	x	x
19	Deferred Treatment Arm Only	Week 28	Predose	x	x
			~2 hrs Postdose	x	x
	Not applicable	Unsched/Viral Failure Conf Visit	NA[3]	x	x
	Not applicable	Early Discon Visit	NA[3]	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] Time Relative to last Dose of MK-5172, MK-8742 must be recorded in INFORM
[3] The date and time of the last MK-5172, MK-8742 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 dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary).

Table 8 Pharmacokinetic Sampling Timepoints- Intensive PK Arm

Visit Number	Study Day/Week	Time Relative to Dose of MK-5172, MK-8742[2]	MK-5172 PK Sample[1]	MK-8742 PK Sample[1]
2	Day 1[4]	Predose	x	x
6	Week 4	Predose	x	x
		0.5	x	x
		1	x	x
		2	x	x
		3	x	x
		4	x	x
		6	x	x
		8	x	x
		12	x	x
		16	x	x
		24	x	x
10	Week 12[4]	Predose	x	x
		~2 hrs Postdose	x	x
	Unsched/Viral Failure Conf Visit	NA[3]	x	x
	Early Discon Visit	NA[3]	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] Time Relative to last Dose of MK-5172, MK-8742 must be recorded in INFORM
[3] The date and time of the last MK-5172, MK-8742 dose prior to each PK sample collected must be recorded in INFORM
[4] Since all subjects will have samples taken on Day 1 and on Week 12 for population PK, additional samples for Intensive PK do not need to be collected.
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 dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary).

Table 9 Pharmacokinetic Sampling Timepoints- Evening Pre-Dose PK Cohort

Visit Number	Study Population	Study Day/Week	Time Relative to Dose of MK-5172, MK-8742[2]	MK-5172 PK Sample[1]	MK-8742 PK Sample[1]
6	Immediate and Deferred Treatment arm	Week 4	Predose	x	x
10	Immediate and Deferred Treatment arm	Week 12[4]	Predose	x	x
			~2 hrs Postdose	x	x
	Not applicable	Unsched/Viral Failure Conf Visit	NA[3]	x	x
	Not applicable	Early Discon Visit	NA[3]	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] Time Relative to last Dose of MK-5172, MK-8742 must be recorded in INFORM
[3] The date and time of the last MK-5172, MK-8742 dose prior to each PK sample collected must be recorded in INFORM
[4] Since all subjects will have samples taken on Week 12 for population PK, additional samples for evening pre-dose PK do not need to be collected
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 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 for genomics use
- Leftover plasma from HCV RNA
- Leftover plasma from viral resistance and biomarkers

7.1.4.4 HCV Evaluation

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

- Samples for HCV Genotype evaluation must be obtained 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™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® assay. Lleftover 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 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.

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

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

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

7.1.5.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.5.2 Blinding/Unblinding

IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety. The emergency unblinding call center will provide after-hours emergency unblinding coverage when the investigator is not available.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.5.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

None

7.1.5.4 Rescreening

- Subjects who have previously completed the screening visit (Visit 1) and were deemed eligible for randomization into this study, but failed to be randomized within the 60-day window, may be rescreened to re-evaluate study eligibility. To reconfirm the subject's eligibility, all pre-study evaluations should be repeated, after approval from the SPONSOR, except for the following:

- HCV GT Determination

- Liver biopsy

- 12-Lead ECG

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

7.1.5.5 PK Sampling Time Points

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

detailed time points of PK sample collection please refer to Table 7, Table 8 and Table 9 in Section 7.1.4.2.1.

7.1.6 Visit Requirements

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

7.1.6.1 Screening

Within 60 days prior to administration of the initial dose of study drug, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Verification should be obtained to confirm that the subject is non-cirrhotic and the subject's fibrosis score must be captured to support secondary data analysis. The primary etiology of the subject's renal disease must be captured. 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 and throughout treatment, 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 Treatment Period Visit

Treatment Day 1 (Visit 2)

Pretreatment Procedures

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

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

Additional samples will be collected for genetic evaluation of host parameters related to the response of HCV subjects to MK-5172 and MK-8742 therapies.

7.1.6.3 Drug Administration

Following completion of the Day 1 procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS for assignment of the drug to be administered. Sites should not call IVRS for drug administration until the subject has met all criteria for the study and are ready to receive the first dose of study medication on Day 1.

The first dose of trial treatment will be taken by the subject in the evening of Day 1 (Visit 2) for all subjects (Immediate Treatment, Deferred Treatment and Intensive PK arms) and in the evening of the Week 16 visit (Visit 10) only for subjects in the deferred treatment arm. Subsequent dosing will be taken in the evenings by the subject at approximately the same time each day (except for Week 12 and Week 28 doses which must be withheld the night before for the predose PK collection at those visits).

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

At the completion of study therapy (see Section 5.6) subjects will return to the study site for follow-up visits at 4, 12, and 24 weeks, after the last dose of study drug. If a subject completes 12 weeks of therapy (immediate treatment arm and intensive PK arm), the 4, 12, and 24 –week follow-up visits will occur approximately 16, 24, and 36 weeks after Day 1, respectively. Similarly, if a subject completes 24 weeks of therapy (deferred treatment arm),

the 4, 12, and 24 –week follow-up visits will occur approximately 28, 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 4, 12, and 24 weeks following the confirmation of virologic failure. Subjects who meet the virologic failure criterion of relapse (having HCV RNA ≥ LLoQ following end of all study therapy, after becoming undetectable (TND) at end of treatment) will return to the study site for follow-up visits at 4, 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 4, 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. Subjects who undergo kidney transplant and either complete or discontinue this study will also be followed in PN017. The purpose of this follow-up protocol is to follow resistance associated variants (RAVs) over time and in the case of treatment responders, to follow durability of response.

7.1.6.5 Evaluations of Laboratory Safety Signals

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

If a subject has one or more of the laboratory ECI criteria (Refer section 7.2.3.2) at the last dosing visit (Week 12 for immediate treatment arm or intensive PK arm or Week 24 for deferred treatment arm), then the subject should return to the site weekly for additional monitoring until the values normalize.

7.1.6.6 Trial Unblinding

For emergency unblinding please refer to Section 7.1.4.4.

Unblinding will occur at Week 16 of the study after all data through Week 12 and safety follow-up after Week 12 have been completed, data cleaned and queries resolved. If the subject is determined to have received active therapy during the first 12 weeks, the visit at Week 16 will be the FU 4 visit and those study procedures should be followed. If the subject

was determined to have received placebo during the first 12 weeks, the visit at Week 16 will be counted as Visit 11 (Day 1 of active dosing) and those study visits followed.

7.2 Assessing and Recording Adverse Events

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

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

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

Adverse events may occur during the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events will be recorded from the time the consent form is signed through 14 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

In this trial, an overdose is any dose higher than: Any intake in excess of the prescribed dose of MK-5172 or MK-8742 per calendar day.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), 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 (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse EventsAdverse Events and Incidents

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 10 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the Sponsor's product, must be

reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. first instance of ALT or AST>500 IU/L from the initiation of study therapy through 14 days following treatment and not associated with virologic failure*

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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 10. The investigator’s assessment of causality is required for each adverse event. Refer to Table 10 for instructions in evaluating adverse events.

Table 10 Evaluating Adverse Events

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse 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.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The DMC will include 3-5 clinicians experienced in hepatology and nephrology and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The DMC will make recommendations to the SPONSOR regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.2.9 - Interim Analyses) and recommend to the SPONSOR if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the SPONSOR; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the SPONSOR regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the

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

The first analysis will contain SVR_4 and SVR_{12} from the immediate treatment and the intensive PK arms and EOT HCV RNA result from the deferred treatment arm; safety analysis will include a comparison of on-treatment safety in immediate vs. deferred treatment group and a summary for the immediate treatment arm on safety parameters and adverse events during the study therapy period or within 14 days after discontinuing study therapy.

The second analysis will include SVR_{24} from the immediate treatment arm and the intensive PK arm, SVR_4, SVR_{12} and SVR_{24} from the deferred treatment arm, and SVR_{12} and SVR_{24} for all treatment arms combined; safety will contain the summary on safety parameters and adverse events during the study therapy period or within 14 days after discontinuing study therapy for the deferred treatment arm and for all three arms combined.

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analysis

The primary efficacy endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 11 below.

Table 11 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}	Wald test	Modified Full Analysis set † (mFAS)	TRD=F

†The mFAS population is a subset of the subjects in the immediate treatment and the intensive PK arms with exclusion of subjects who fail to receive at least one dose of study treatment and subjects with missing data due to death or early discontinuation from the study with reasons unrelated to their responses to the HCV treatment.

‡ TRD=F: Treatment-Related Discontinuation = Failure (missing values due to death with reasons related to study drug or liver disease, and missing values due to premature study discontinuations with treatment related reasons such as, clinical or laboratory adverse event related to the study drug, or lack of efficacy are considered as failures thereafter)
Additional details provided in Section 8.2.

The primary hypothesis is that patients treated with MK-5172 + MK-8742 for 12 weeks will achieve a SVR_{12} rate higher than the reference SVR_{12} rate of 45%. The hypothesis will be evaluated within the subjects of the immediate treatment and the intensive PK arms, and it will be tested at two-sided significant level (type-I error) of 0.05. A 95% asymptotic (Wald) confidence interval (CI) will also be constructed for the SVR_{12} rate.

Several considerations led us to choose a reference SVR of 45% for this study:

(1) IFN mono-therapy is recommended for HCV-infected patients with CKD stages 3-5 who are on or not yet on maintenance dialysis therapy [19]. The meta-analyses, conducted by Fabrizi et al, revealed a summary SVR_{24} of 39% (CI 32%-46%) [20].

(2) Given the substantial variation in the GT1 proportion of the studies (ranging from 0 to 1) in the Fabrizi meta-analyses, a Bayesian logistic regression model for SVR was used to account for the variation of GT1 proportions. Twenty studies with GT1 proportion were identified from the Fabrizi paper and included in the re-analysis. Non-informative priors were used for the Bayesian random-effect model containing a random intercept and a fixed-effect of GT1 proportion. The model predicts that, if the studies had enrolled 100% GT1, the posterior probability/confidence that the true overall population mean for SVR rate would have been at most 45% is about 0.90.

(3) A SVR of approximately 40% was observed in a large study of PEG-IFN/RBV in 3,070 HCV GT1 patients without renal disease conducted in the United States [28]. The SVR response of patients with CKD stage 4-5 is not expected to be higher than that of the general HCV population without renal disease.

8.1.2 Safety Analysis

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: adverse events of elevated laboratory values that are reported as ECIs described in section 7.2.3.2 (Tier 1 events). The Tier 1 events rates of the immediate treatment arm will be compared to those of the placebo treatment period of the deferred treatment arm. P-values and 95% confidence intervals for between-treatment differences will be calculated using the Miettinen and Nurminen method [29].

Safety and tolerability will be carefully monitored throughout the study by the SPONSOR (or designee) in accordance with standard procedures and also by an external Data Monitoring Committee (DMC).

8.1.3 Power and Sample Size

This study will randomize 105 subjects into the immediate treatment arm and 105 subjects into the deferred treatment group. In addition, 10 subjects will be enrolled as intensive PK cohort. The primary hypothesis will be evaluated within the subjects of the immediate treatment and the intensive PK arms (n=115). It would have at least 95% power to

demonstrate that the SVR_{12} rate of MK-5172 + MK-8742 is higher than the reference SVR_{12} rate of 45% at an overall one-sided 0.025 α-level, if the true SVR_{12} rate of MK-5172 + MK-8742 is about 65%. The power and sample size are based on the assumption that approximately 10% of the randomized subjects would have missing SVR_{12} rate due to death or early discontinuation from study with reasons unrelated to their responses to the HCV treatment and will be excluded from the mFAS population (i.e. assuming the mFAS population size of 103 subjects). The calculation is based on SAS PROC POWER based on z-test using the normal approximation to the binomial distribution.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

Subjects in the immediate and deferred treatment arms, and corresponding site personnel and investigators will remain blinded to the treatment groups for the first 12 weeks of treatment period under in-house blinding procedures. The second 12 weeks of active treatment period for the deferred arm will be conducted as an open-label study. The database will be unblinded at Week 16 visit for the immediate and the deferred treatment arm. Note that the Week 16 visit takes place 16 weeks after randomization, and it is also the FU WK4 visit for the immediate treatment arm.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented by an IVRS. (Please note, the 10 subjects assigned to the Intensive PK Arm will be open-label)

Pharmacokinetic (PK) measurements will be conducted in support of PK evaluations. Additionally, a small team as specified in a separate Modeling and Simulation (M&S) Modeling Analysis Plan, and who are separate from the study team, will be unblinded for the purpose of preparing the pharmacokinetic analyses. No PK data or results from the PK analyses will be shared with the study team, and the unblinded group will not be members of the study team.

During the course of the trial, periodic safety analyses will be conducted. An external data monitoring committee (DMC) will be established to safeguard the interests of trial participants, to provide ongoing review of those safety data and to monitor the overall conduct of the trial.

For the first 12 weeks of treatment period, treatment-level and patient-level safety results will be provided by the unblinded statistician to DMC. Limited additional SPONSOR personnel may be unblinded to the treatment level results of these reviews, if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with

respect to results of interim reviews will be documented by the unblinded statistician. The unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses.

The DMC will perform periodic reviews of safety data in order to protect subject welfare and preserve study integrity. There will be no enrollment pause in the study during these reviews. The DMC is to recommend to the SPONSOR whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. While the DMC will be asked to advise SPONSOR regarding future conduct of the study, including possible early study termination, SPONSOR retains final decision-making authority on all aspects of the study. Additional logistical details will be provided in the external DMC Charter.

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 SVR_{12} rate of the subjects in the immediate treatment and the intensive PK arms.

The secondary efficacy endpoints are

1. The SVR_4 and SVR_{24} rates of the subjects within the immediate treatment and the intensive PK arms.
2. The SVR_4, SVR_{12}, and SVR_{24} rates in the deferred treatment arm following the end of all active study therapy.
3. The SVR_4, SVR_{12}, and SVR_{24} rates following the end of all active study therapy for all treatment arms combined.
4. The emergence of viral resistant to MK-5172 and MK-8742 when administered as a combination regimen
5. Proportion of achieving TND, TD(u), and TD(q) at EOT

8.2.3.1.2 Pharmacokinetic Endpoints

An initial description of efficacy measures is provided in Section 4.2.3.3.

The PK endpoints for MK-5172, MK-8742 are AUC_{0-24}, C_{2hr} and C_{trough}

8.2.3.1.3 Exploratory Endpoints

1. The level of biomarkers (e.g., proteins and metabolite production), that may be predictive of tolerability of study drugs and virologic response to MK-5172 in combination with MK-8742

2. 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) score

3. Change from baseline in Serum cryoglobulin level, rheumatoid factor, and C4 Complement in subjects with Cryoglobulinemia

8.2.3.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.2.

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified *a priori* constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters (requires that at least 4 subjects in each treatment group exhibit the event) will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

For this protocol, the Tier 1 safety parameters and adverse events are the proportion of subjects with adverse events of the following types at any time during the study therapy period: adverse events of elevated laboratory values that are reported as ECIs described in section 7.2.3.2.

The following are Tier 2 safety parameters and adverse events:

1. Proportion of subjects with adverse experiences 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 renal serious adverse event; (5) a serious and drug-related adverse event; (6) an adverse event leading to discontinuation from treatment; and (7) renal disease progression (defined as increasing dialysis frequency in subjects who were on hemodialysis at baseline, initiation of maintenance hemodialysis in subjects who were not on hemodialysis at baseline, or progressive increase in CKD stages).

2. Change from baseline in serum creatinine and BUN, estimated GFR at the end of active study therapy for the immediate treatment arm and at the end of placebo treatment for the deferred treatment arm for CKD 4-5 subjects who are not receiving HD at baseline.

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

For all subjects in the deferred treatment arm, safety results during the period of receiving active study therapy will be summarized and described.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Modified Full Analysis Set (mFAS) population will serve as the primary population for the analysis of efficacy data in this study. The mFAS population is a subset of the subjects, who are randomized to the immediate treatment arm or who are assigned to the intensive PK arm, with subjects excluded for the following reasons:

- failure to receive at least one dose of study treatment
- missing data due to death with reasons unrelated to study drug or reasons other than liver disease
- missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug and their responses to the HCV treatment.

All subjects who return for follow-up visits will be included in the corresponding SVR analysis, regardless of the length of treatment received or reason for discontinuation.

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary (SVR_{12}) and key secondary efficacy endpoints (SVR_4 and SVR_{24}). The PP population is a subset of the mFAS population. 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 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
- The subject met criteria for futility, virologic breakthrough or end of treatment failure but had undetectable MK-5172 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 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-5172 leads to a clinically significant lowering of MK-5172 concentrations

- Other violations may be identified during the course of data collection and they will be listed specifically in the CSR

A subject with important deviations from the protocol as described above at 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.

The FAS population consists of all randomized subjects who have received at least one dose of study treatment. This is one of the supportive analysis populations in this study.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using mFAS, 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. Statistical testing and inference for safety analyses are described in Section 8.2.5.2. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.2.5.1 Statistical Methods for Efficacy Analyses

Missing values

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

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

1. Intermittent missing: If a missing data point is immediately preceded and followed by non-missing HCV RNA outcomes, the missing value would be imputed to the worse outcome of the two. For example, if a missing data point is preceded by TD(q) and followed by TD(u) or TND, then the missing value would be imputed as TD(q); if a missing data point is preceded by TD(u) and followed by TND, then the missing value would be imputed as TD(u); when a missing value is flanked by two TND, then the missing value would be imputed as TND.

2. Non-intermittent missing related to the study drug: For missing values due to death with reasons related to study drug or liver disease, and missing values due to premature study discontinuations with treatment related reasons such as, progression of liver disease, clinical or laboratory adverse event related to the study drug, or lack of efficacy (e.g. discontinuation from the study following a confirmed HCV RNA TD(q)), the missing values will be considered as treatment failures and thereafter.

3. Non-intermittent missing unrelated to the study drug: For missing data due to death with reasons unrelated to study drug or reasons other than liver disease, and due to premature study discontinuations with reasons unrelated to treatment such as loss to follow-up, protocol violation, patient withdrew consent, etc., the missingness mechanism is unlikely to related to patients' response to the HCV treatment, and therefore the missing at random (MAR) assumption is plausible. The approaches to address this type of missing data depend on the analytical strategy, and they are described in the following sections.

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

SVR_{12} rate (proportion of achieving SVR_{12})

The study hypothesis is that patients treated with MK-5172 + MK-8742 for 12 weeks will achieve a SVR12 rate higher than the reference SVR12 rate of 45%. Correspondingly, the null hypothesis (H_0) is that SVR_{12} rate $\leq$ 45%; the alternative hypothesis (Ha) is that SVR_{12} rate $>$ 45%. A treatment effect is established statistically by showing that the lower bound of the two-sided 95% confidence interval for SVR_{12} rate > 45%. A Wald test will be performed

at two-sided significant level (type-I error) of 0.05. This hypothesis will be evaluated primarily in the combined immediate treatment and intensive PK arms.

Primary approach

The SVR_{12} rate is estimated by the ratio of the number of subjects achieving SVR_{12} versus the number of subjects in the mFAS population, that is, the proportion of subjects with SVR_{12} in the mFAS. A two-sided 95% asymptotic (Wald) confidence interval will be calculated. Under the assumption of missing completely at random (MCAR), the mFAS population excludes subjects who did not experience virologic failure, but prematurely withdraw from study due to reasons not related to the study drug (i.e., the subjects with the type 3 missing value) . Note that subjects with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are included in the mFAS population and classified as failures.

Secondary approaches

The SVR_{12} rate will also be estimated in the PP population as supportive analysis, using the approach described above.

Sensitivity analysis will be conducted in the FAS population to address the robustness of the study conclusion to the management of the type 3 missing information. In this analysis, the type 3 missing will be imputed as failure. The SVR_{12} rate is estimated by the ratio of the number of subjects achieving SVR_{12} versus the number of subjects in the FAS population, that is, the proportion of subjects with SVR_{12} in the FAS. However, it is useful to note that this approach invokes maximal stress to the robustness of the study results and puts a bound on the extent of the impact of the type 3 missing information.

Other efficacy endpoints

The EOT HCV RNA for the immediate treatment and intensive PK arms and for the deferred treatment arm will be summarized as proportion according to the categories of TND, TD(u), and TD(q). Table 12 summarizes the key efficacy analyses.

Table 12 Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Time point)	Primary vs Secondary Approach[†]	Statistical Method	Analysis Population	Approach for Non-Intermittent Missing Data
Primary:				
SVR_{12} rate	P	Wald test (95% asymptotic CI)	mFAS	TRD=F[‡] (i.e., M=F[‡] for type 2 DAO [‡] for type 3
SVR_{12} rate	S	Wald test (95% asymptotic CI)	FAS	M=F for type 2 and type 3
SVR_{12} rate	S	Wald test (95% asymptotic CI)	PP	TRD=F (i.e., M=F for type 2 DAO for type 3)
Secondary				
SVR_4 and SVR_{24} rates	P	95% asymptotic CI	mFAS	TRD=F (i.e., M=F for type 2 DAO for type 3
SVR_4 and SVR_{24} rates	S	95% asymptotic CI	FAS	M=F for type 2 and type 3
SVR_4 and SVR_{24} rates	S	95% asymptotic CI	PP	TRD=F (i.e., M=F for type 2 DAO for type 3

[†] P=Primary approach; S=Secondary approach.
[‡] Imputation for specific missing values described in Section 8.2.5.1
TRD=F is Treatment-Related Discontinuation = Failure; DAO = Data as observed; M=F is missing=failure

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

Summary statistics will be provided to describe the rates of occurrence of subject virologic non-response, rebound, breakthrough, and relapse. Definitions for subject virologic non-response, rebound, breakthrough, and relapse are in Section 4.2.3.1.1.2

8.2.5.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as endpoints of special

interest will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Changes from baseline in laboratory and vital signs that are not pre-specified as endpoints of special interest will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format.

Values for missing safety laboratory data or missing vital signs will not be imputed; however, a missing Baseline/Day 1 result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the Baseline/Day 1 value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities. Missing values will be handled using the Data-As-Observed (DAO) approach.

For this protocol, the primary safety analysis will compare the safety data in the immediate treatment arm during the treatment period to those of the deferred treatment arm during the placebo treatment period. For categorical data, p-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen method [29], an unconditional, asymptotic method. For continuous data (as Tier 2), 95% confidence intervals will be provided for differences in the group means using asymptotic method

The safety parameters and adverse events during the active study therapy period, or within 14 days after discontinuing active study therapy will also be summarized for the combined immediate treatment and intensive PK arms, and for the differed treatment arm. 95% CI will be provided for the proportion of subjects with the Tier 1 and Tier 2 adverse events.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	AEs of elevated laboratory values that are reported as ECIs	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Renal SAE		X	X
	Discontinuation due to AE		X	X
	Renal disease progression		X	X
	Change from Baseline Results (serum creatinine, BUN, and estimated GFR)		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 of patients in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs, or PDLCs‡ (incidence < 4 of patients in one of the treatment groups)			X
	Change from Baseline Results (Labs and Vital Signs)			X

† Adverse events references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specifed as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

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 statistics. 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 arm 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 and MK-8742 will be provided for the immediate treatment and the intensive PK groups. PK/PD analysis may also be performed within the intensive PK and evening pre-dose PK cohorts for MK-5172 and MK-8742.

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 SVR_{12} 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

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 for the immediate and deferred treatment arms at Week 12, Week 28 (deferred treatment arm only), Follow-Up Week 12, and Early Discontinuation. 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.

8.2.6 Multiplicity

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

8.2.7 Sample Size and Power Calculations

8.2.7.1 Efficacy Analysis

This study will randomize 105 subjects into the immediate treatment arm and 105 subjects into the deferred treatment group. In addition, 10 subjects will be enrolled as intensive PK cohort. The primary hypothesis will be evaluated within the subjects of the immediate treatment and the intensive PK arms (n=115). It would have at least 95% power to demonstrate that the SVR_{12} rate of MK-5172 + MK-8742 is higher than the reference SVR_{12} rate of 45% at an overall one-sided 0.025 α-level, if the true SVR_{12} rate of MK-5172 + MK-8742 is about 65%. The power and sample size are based on the assumption that approximately 10% of the randomized subjects would have missing SVR_{12} rate due to death or early discontinuation from study with reasons unrelated to their responses to the HCV treatment and will be excluded from the mFAS population (i.e. assuming the mFAS

population size of 103 subjects). The calculation is based on SAS PROC POWER based on z-test using the normal approximation to the binomial distribution. Table 14 summarizes such power calculations for the primary efficacy analysis under various assumptions about the true SVR_{12} rate of MK-5172 + MK-8742.

Table 14 Power Calculations for the Primary Hypothesis Test Within the Subjects of the Immediate Treatment and the Intensive PK Arms

True SVR_{12} rate	Power to reject H_0
60%	86%
62%	93%
65%	98%
70%	>99%

8.2.7.2 Safety Analysis

The primary safety analysis will compare the safety data in the immediate treatment arm during the treatment period to those of the deferred treatment arm during the placebo period. Table 15 summarizes the power to detect an adverse event rate difference between the treatment arms using a 2-sided 5% alpha level, if the immediate treatment arm has a two-fold or three-fold increment in adverse event rate. These calculations are under various assumptions about the true adverse event rate in the deferred treatment arm, and assume 105 subjects in each arm.

Table 16 gives the power to rule out a 50% or 100% higher adverse event rate in the immediate treatment arm at a 1-sided 2.5% alpha level, if the event rates are the same in both the immediate and deferred treatment arms. The calculations assume 105 subjects in each arm and are based on an asymptotic method proposed by Farrington and Manning (1990).

Table 15 Power to Detect Difference in Adverse Event Rate

True event rate in the deferred arm while placebo administered	True event rate in The Immediate treatment arm	Power to detect difference (at a 2-sided 0.05 α-level)
Two-fold increment		
10%	20%	53%
15%	30%	74%
20%	40%	89%
25%	50%	97%
Three-fold increment		
10%	30%	96%
15%	45%	99%
20%	60%	>99%
25%	75%	>99%

Table 16 Power to Rule Out a 50% or 100% Higher Adverse Event Rate in the Immediate Treatment Arm, Assuming Both Arms Have the Same Event Rate

True event rate in both immediate and deferred arms	Power to rule out a 50% increase in the immediate treatment arm	Power to rule out a 100% increase in the immediate treatment arm
10%	21%	63%
15%	32%	84%
20%	43%	95%
25%	55%	99%
30%	66%	> 99%

8.2.8 Subgroup Analyses and Effects of Baseline Factors

To determine whether the response is consistent across various subgroups, the SVR_{12} rate with 95% CIs will be estimated within each category of the following classification variables:

- Sex (female, male)
- GT: (1a vs 1 non-a)
- *IL28B* CC genotype vs. non-CC genotype
- HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL)
- Stage of fibrosis (Non-cirrhotic vs. Cirrhotic)
- Dialysis (yes vs. no)
- Diabetes (yes vs. no)
- CKD stage (4 and 5)
- Prior IFN or PEG-IFN ± Ribavirin treatment response (Treatment naïve, Relapser, Partial responder, and Null Responder)

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

In addition, Safety comparison between the immediate and differed treatment arms will also be conducted according to the subgroups of on dialysis vs. not on dialysis, diabetics vs. non-diabetics, and CKD stages (4 and 5).

8.2.9 Interim Analyses

No formal interim analyses are planned for this study. During the course of the trial, periodic safety analyses will be conducted for the accruing data and will be reviewed by an external DMC at regular intervals to ensure the safety of the patients participating in the clinical trial.

8.2.10 Compliance (Medical Adherence)

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

A day within the study will be considered an "On-Therapy" day if the subject takes the MK-5172 100mg/MK-8742 50mg or the Placebo tablet(s). The "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study medication for that subject. Note, the date of the last dose of study medication would be the last scheduled day for treatment administration for subject who completed the assigned treatment.

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

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

Summary statistics will be provided on percent compliance.

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 17.

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

Table 17 Product Descriptions

Product Name & Potency	Dosage Form
MK-5172 100mg	Tablet
MK-5172 0mg	Tablet
MK-8742 50mg	Tablet
MK-8742 0mg	Tablet
MK-5172 100mg / MK8742 50mg	Tablet
MK-5172 0mg / MK8742 0mg	Tablet

All placebos were created by the Sponsor to match the active product.

The single entity tablet formulations will be used in the Intensive PK arm and for the first 12 weeks of dosing in the Immediate Treatment and Deferred Treatment arms. The fixed dose combination formulation will be used for Week 16 to Week 28 dosing in the Deferred Treatment arm.

9.2 Packaging and Labeling Information

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

Subjects will receive open label and blinded monthly finished good bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

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

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

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

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 treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

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

10.7 Publications

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

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

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

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

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

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

11.0 LIST OF REFERENCES

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