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Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-naïve or Previously Treated Patients with HCV Genotype 1 or 3 Infections

Short title: Sofosbuvir-Velpatasvir plus GS-9857 for HCV

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ABBREVIATIONS

HCV, hepatitis C virus; DAA, direct-acting antiviral agent; SVR, sustained virologic response; SOF, sofosbuvir; VEL, velpatasvir; PEG+RBV, pegylated interferon plus ribavirin; SVR12, sustained virologic response 12 weeks post therapy; RAS, resistance-associated substitution

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AUTHOR DISCLOSURES

EJG: Grant/Research – Gilead; Advisory Board – AbbVie, Boehringer Ingelheim, Gilead, Janssen, Novartis, Roche, Tibotec; Speaker – Gilead, Novartis, Roche, Tibotec; Patents – Gilead. **CS:**

Grant/Research – Gilead. **CAS:** Grant/Research – Gilead; Advisory Board – Janssen, Roche, AbbVie, Gilead, MSD. All other authors are current employees of Gilead Sciences.

AUTHOR CONTRIBUTIONS

EJG, RHH, LMS, DMB and JGM contributed to the conception and design of the study. EJG, CS, CAS, RHH, YY, ES, LMS, DMB and JGM contributed to the generation, collection, assembly, analysis and/or interpretation of data. All authors contributed to drafting or revision of the manuscript, and all approved the final version of the manuscript.

WRITING ASSISTANCE

Writing assistance was provided by David McNeel of Gilead Sciences.

Trial registration details: NCT02202980 (ClinicalTrials.gov)

ABSTRACT

Background & Aims: We performed a phase 2 trial of the efficacy and safety of 4, 6, and 8 weeks of sofosbuvir, given in combination with the NS5A inhibitor velpatasvir and the NS3/4A protease inhibitor GS-9857, in patients with hepatitis C virus (HCV) infection.

Methods: We enrolled 161 treatment-naïve or previously treated patients infected with HCV genotypes 1 or 3 with or without compensated cirrhosis at 2 centers in New Zealand, from September 2014 through March 2015. All patients received sofosbuvir (400 mg) and velpatasvir (100 mg) plus GS-9857 (100 mg) once daily. The primary efficacy endpoint was sustained virologic response at 12 weeks after therapy (SVR12). The duration of therapy was determined by baseline patient characteristics: 4 or 6 weeks for treatment-naïve patients without cirrhosis, 6 weeks for treatment-naïve patients with cirrhosis, and 6 or 8 weeks for treatment-experienced patients with or without cirrhosis.

Results: Four weeks of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in 4/15 (27%) treatment-naïve patients with HCV genotype 1 without cirrhosis. Six weeks of this combination produced a SVR12 in 14/15 (93%) treatment-naïve patients with HCV genotype 1 without cirrhosis, in 13/15 (87%) treatment-naïve genotype 1 patients with cirrhosis, in 15/18 (83%) treatment-naïve patients with HCV genotype 3 with cirrhosis, and in 20/30 (67%) patients with HCV genotype 1 who had failed an all-oral regimen of 2 or more direct-acting antiviral agents (DAAs). Eight weeks of the drug combination produced an SVR12 in 17/17 (100%) patients with HCV genotype 1, in 19/19 (100%) patients with HCV genotype 3 and cirrhosis who had failed peg-interferon plus ribavirin, in 25/28 (89%) patients with HCV genotype 1 who had failed protease inhibitor-based triple therapy, and in 4/4 (100%) patients with HCV genotype 3 who had failed an all-oral regimen of 2 or more DAAs. The most common reported adverse events were headache, nausea, and fatigue.

Conclusions: Eight weeks of treatment with the combination of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in most treatment-naïve or previously treated patients with HCV genotype 1 or 3 infections, including those with compensated cirrhosis. ClinicalTrials.gov number: NCT02202980.

KEY WORDS: clinical trial, LEPTON, difficult to treat, time of treatment

INTRODUCTION

In recent years, the introduction of drugs that selectively target replication of the hepatitis C virus (HCV) has transformed the treatment of patients chronically infected with HCV.[1-4] Combination regimens of direct-acting antiviral agents (DAAs) provide rates of sustained virologic response (SVR) in excess of 90% for most patient populations, even historically difficult-to-treat subpopulations, such as previously treated patients with genotype 3 HCV and cirrhosis. Nevertheless, medical questions remain unaddressed, including the feasibility of shortening duration of treatment through the addition of another antiviral agent, and the identification of the optimal retreatment regimen for patients who have failed prior therapy with approved combinations of DAAs.

Sofosbuvir (SOF) is a uridine nucleotide analogue inhibitor of the HCV NS5B polymerase that is approved in combination with other antivirals to treat patients with HCV infection of every genotype.[5] Velpatasvir (VEL) is an inhibitor of the HCV-encoded NS5A protein, which is essential for HCV RNA replication, post-replication assembly, and secretion.[6] In phase 3 clinical trials, the combination of sofosbuvir and velpatasvir was highly effective in a broad range of patients, including those infected with every genotype, those with compensated and decompensated cirrhosis, and those who did not achieve SVR after prior treatment with other DAA regimens.[7-9] GS-9857 is an experimental macrocyclic HCV NS3/4A protease inhibitor with potent in vitro antiviral activity against genotype 1 to 6 HCV, broad coverage of NS3/4A protease polymorphisms, and a resistance profile that compares favourably with that of other protease inhibitors (J Taylor et al, J Hepatol 62:S681, Abstract; B Kirby et al, J Hepatol 62:S663, Abstract; M Rodriguez-Torres et al, J Hepatol 62:S673, Abstract).

We report results from eight arms of the LEPTON trial. These arms were designed to evaluate the safety and efficacy of short duration regimens of SOF/VEL plus GS-9857 in a broad range of

patients with genotype 1 and 3 HCV infection. The primary efficacy endpoint was sustained virologic response, defined as HCV RNA below the limit of detection (15 IU/mL) 12 weeks after the end of therapy (SVR12).

METHODS

Patients

We enrolled patients at two centers in New Zealand from September 2014 to March 2015 (clinicaltrials.gov, number NCT02202980). Eligible patients were men and women 18 years of age and older, with chronic genotype 1 or 3 HCV infection (serum HCV RNA $\geq 10^4$ IU/mL) and a body mass index of at least 18 kg/m^2. Cirrhosis was defined as a biopsy showing cirrhosis, transient elastography score of >12.5 kPa, or a FibroTest score of >0.75 and an AST: platelet ratio index of >2 during screening. Patients with hepatic decompensation were excluded.

Six groups of patients with genotype 1 HCV and three groups of patients with genotype 3 HCV were enrolled. The six groups of patients with genotype 1 HCV consisted of two groups of treatment-naïve patients without cirrhosis, one group of treatment-naïve patients with cirrhosis, one group of patients with cirrhosis who had failed treatment with pegylated IFN plus ribavirin (PEG+RBV)**,** one group of patients with and without cirrhosis who had failed treatment with a protease inhibitor plus PEG+RBV, and one group of patients with and without cirrhosis who had failed treatment with a DAA-containing regimen with or without PEG+RBV. The three groups of patients with genotype 3 HCV consisted of one group of treatment-naïve patients with cirrhosis, one group of patients with cirrhosis who had failed treatment with PEG+RBV and one group of patients with and without cirrhosis who had failed treatment with a DAA-containing regimen with or without PEG+RBV.

Study Design

All patients in this open-label study received sofosbuvir (400 mg) and velpatasvir (100 mg) in a fixed-dose combination (SOF/VEL) and GS-9857 100 mg (Gilead Sciences, Foster City, California), administered orally once daily with food. According to the original design for this cohort, one group of treatment-naïve patients with genotype 1 HCV received 4 weeks of treatment and the other eight groups were to receive six weeks of treatment. However, following suboptimal outcomes in the first treatment-experienced group which included patients who had failed a DAA-containing regimen, the protocol was amended to extend the duration of therapy to eight weeks in the remaining treatment-experienced groups**.** In all, one group received 4 weeks of treatment, four groups received 6 weeks of treatment, and four groups received 8 weeks of treatment (Figure 1).

Study Assessments

Serum HCV RNA levels were measured with the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 with a lower limit of quantitation of 15 IU/mL. HCV genotype and subtype were determined using the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 Assay. At each study visit, vital signs were measured and electrocardiograms and symptom-directed physical examinations were conducted; in addition, blood and urine samples were taken for laboratory assessments. All adverse events were recorded and graded according to standardized scales.

For analysis of viral resistance, serum or plasma samples obtained at each time point were stored for drug resistance monitoring. Deep sequencing (assay cut-off at 1%) of the full-length NS3/4A, NS5A, and NS5B region was performed on baseline samples for all patients, as well as samples taken at time of virologic failure for patients who did not achieve SVR due to virologic failure or early discontinuation, and who had HCV RNA ≥1000 IU/mL.

End Points and Statistical Methods

The primary efficacy end point was the rate of sustained virologic response, defined as the absence of quantifiable HCV RNA in serum (<15 IU/mL) at 12 weeks after the end of therapy (SVR12) among all patients who underwent randomization and received at least 1 dose of study drugs. The proportions of patients with SVR12 along with a 2-sided 95% confidence interval (using the binomial distribution) were calculated by group and treatment duration. This open-label study was not designed to evaluate formal statistical hypotheses, and no sample size calculations were performed. The sample size was based on practical considerations. The primary safety endpoint is any adverse event leading to permanent discontinuation of study treatment.

Study Oversight

All patients provided informed consent. The study was approved by the institutional review board at both participating sites and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study was designed and conducted by the sponsor in collaboration with the principal investigators. The sponsor collected the data and monitored the study conduct. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All authors had access to the study data and reviewed and approved the final manuscript.

Role of the Funding Source

The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. An independent data and safety monitoring committee reviewed the progress of the study. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. The first draft of the manuscript was prepared by a professional writer who is an employee of Gilead Sciences and the lead author, with the final version incorporating input from all authors.

RESULTS

Patient Characteristics

Of the 213 patients who were screened, 161 were enrolled and commenced treatment, including 120 patients with genotype 1 HCV and 41 with genotype 3 HCV (Supplementary Table 1). All 161 patients completed treatment and were assessed for efficacy and safety. Table 1 shows demographics and baseline characteristics by treatment group. The majority of patients were male and white. No African-American patients were enrolled, which was not unexpected given that the trial was conducted in New Zealand, where less than 1% of the population are African-American. Fifty-four per cent of patients had compensated cirrhosis and 61% had received previous treatment for HCV.

The patients with HCV genotype 1 who had failed treatment with a DAA-containing regimen had all previously been treated with DAAs from at least two classes: protease inhibitor plus an NS5B nucleotide polymerase inhibitor for 20 patients; protease inhibitor plus non-nucleoside NS5B polymerase inhibitor plus for 6 patients; NS5A inhibitor plus NS5B nucleotide polymerase inhibitor for 4 patients. Two patients in the DAA-experienced genotype 3 group had previously received a NS5A inhibitor plus nucleotide polymerase inhibitor, one had received a nucleotide polymerase inhibitor with peginterferon-ribavirin and one had received an NS5A inhibitor with peginterferon-ribavirin (Supplementary Table 2).

Virologic Response

On-treatment virologic response

By week 4 of treatment, serum HCV RNA was <15 IU/mL in all 63 treatment-naïve patients, and in 85 of the 98 previously treated patients (87%). All but three of the 161 patients (98%) had serum HCV RNA <15 IU/mL by week 6 of treatment (Table 2).

Sustained virologic response

Rates of SVR12 by treatment group are shown in Table 2. Among treatment-naïve patients with genotype 1 infection without cirrhosis, SVR12 was achieved in 4 of 15 (27%) receiving SOF/VEL

plus GS-9857 for four weeks and in 14 of 15 (93%) receiving SOF/VEL plus GS-9857 for six weeks. Of the 15 treatment-naïve patients with genotype 1 HCV and cirrhosis receiving six weeks of treatment, 13 (87%) achieved SVR12. Six weeks of treatment led to SVR12 in 20 of 30 (67%) patients with and without cirrhosis who failed previous treatment that contained two DAAs. Eight weeks of SOF/VEL plus GS-9857 led to SVR12 in 17 of 17 (100%) of patients with cirrhosis and with genotype 1 HCV who had previously been treated with PEG+RBV, and in 25 of 28 (89%) patients with or without cirrhosis and with genotype 1 HCV who failed a previous protease inhibitor-containing regimen.

Among treatment-naïve patients with genotype 3 HCV and cirrhosis, SVR12 was achieved by 15 of 18 (83%) receiving six weeks of treatment. Eight weeks of SOF/VEL plus GS-9857 led to SVR12 in 19 of 19 (100%) of patients with cirrhosis and with genotype 3 HCV who had previously been treated with PEG+RBV and in 4 of 4 (100%) of patients with or without cirrhosis and with genotype 3 who failed a previous DAA-containing regimen.

This study was not powered to detect significant differences in rates of SVR by on-treatment viral kinetics, and we therefore cannot make any definitive statements regarding any such association. However, any relation between early viral suppression and SVR does not appear to be strong enough to be clinically useful in predicting response (Supplementary Table 3).

Virologic failure

A total of 30 patients did not achieve SVR12. Of these, 28 had virologic relapse after completing treatment, one withdrew consent after post-treatment week 4 (at which time-point, the patient had undetectable HCV RNA) and one never had HCV RNA below 15 IU/mL on treatment. This last patient was a DAA-experienced 61-year-old male Pacific Islander with genotype 1 HCV and cirrhosis who received six weeks of treatment. This patient's HCV RNA levels declined at every treatment visit but did not become undetectable until post-treatment week 2, and he experienced virologic relapse four weeks after completing treatment.

The observed relapse rate was 73% (11/15) in the patients who received only 4 weeks of treatment, 19% (15/78) in the patients who received 6 weeks of treatment and only 4% (3/68) in those who received 8 weeks of treatment.

Resistance-associated substitutions

Overall, resistance-associated substitutions (RASs) forming at least 1% of the viral population in at least one of the three target genes—NS3, NS5A, and NS5B—were detected at baseline in 76 of 161 (47%) patients. When a 15% threshold was applied, RASs were detected in 57 of 161 (35%) patients. Overall, the SVR12 rate in patients with RASs was 84% (63/75) at the 1% threshold and 86% (48/56) at the 15% threshold, which was similar to the SVR12 rate of 81% (68/84) in patients without RASs. No specific baseline NS3, NS5A, or NS5B RAS alone or in combination predicted virologic failure, even for those patients with prior treatment experience (Supplementary Tables 4 and 5). Specifically, in the patients who had failed previous protease-inhibitor-based therapy, NS3 RASs were detected in 15 of 28 (54%). Of note, 13 of these 15 patients achieved SVR12. In the cohort of patients who had failed previous combination DAA therapy, 7 had received an NS5A inhibitor. NS5A RASs were detected in 6 of 7 (86%) of these patients, of whom 5 (83%) achieved SVR12.

No treatment-emergent NS3, NS5A, or NS5B RASs were detected in 26 of 28 patients who relapsed. Fifteen of these patients had no RASs at baseline and at the time of virologic failure, six patients had re-emergence of baseline RASs at virologic failure (NS3 RASs in 5; NS5A RASs in 2, and both in 1) and five patients baseline RASs (NS3 RASs Q80L, Q168K, or NS5A RASs M28V, Q30H/Y93H, and Q30R/Y93H) had no detectable RASs at virologic failure. Two of 28 patients with virologic failure developed RASs at relapse: NS3 RAS V55A emerged at 2% of the viral population at the time of relapse in one patient who was treatment naïve and received 6 weeks of treatment; NS5B RAS Y93H emerged at 2% of the viral population at the time of relapse in

addition to the pre-existing NS3 RAS R155K in the other patient who was PI-experienced and received 8 weeks of treatment.

Safety & Tolerability

The most common adverse events were headache, nausea, fatigue, and diarrhea (Table 3). Most of the adverse events were mild in severity, and no patient discontinued treatment due to an adverse event. In total, three patients experienced treatment-emergent serious adverse events. Two of the serious adverse events were malignant neoplasms, both in PEG+RBV-experienced patients with HCV genotype 3 and cirrhosis: one 60-year-old white male with cirrhosis who had screening imaging which was non-diagnostic for malignancy was diagnosed with hepatocellular carcinoma on follow-up day 24 and one 59-year-old white male was diagnosed with bladder transitional cell carcinoma on follow-up day 17. Both of these patients achieve SVR12 and the one with hepatocellular carcinoma subsequently underwent liver transplantation without HCV recurrence. The other serious adverse event was in a protease inhibitor-experienced 57-year-old white male with HCV genotype 1 and cirrhosis receiving 8 weeks of treatment, who had moderately severe atrial fibrillation with concurrent non-serious dizziness, fatigue, and headache on day 3 of treatment in the context of strenuous exercise and dehydration. This patient's records indicate that he may have experienced palpitations before starting the study drugs. After treatment with single dose of intravenous amiodarone administered prior to the warning of the use of amiodarone with sofosbuvir-containing regimens, the patient underwent cardioversion and remained in sinus rhythm thereafter. Chronic antiarrhythmics were not initiated and study drug dosing was not interrupted. This event was considered resolved on Day 4.

Grade 3 laboratory abnormalities occurred in 15 (9%) of patients and grade 4 laboratory abnormalities in 3 (2%) of patients overall (Table 3). The only individual grade 3 or 4 laboratory abnormalities reported in more than 5% of patients were grade 3 elevations in serum glucose in six patients (4%) with known diabetes and asymptomatic, and grade 3 elevations in lipase, also in six

patients (4%). Five patients had singular transient grade 3 lipase elevations, all of which decreased upon subsequent testing; the sixth patient with grade 3 lipase elevations through week 6 of treatment had chronic pancreatitis.

DISCUSSION

In this Phase 2 study, the nucleotide polymerase inhibitor SOF with the next generation NS5A inhibitor VEL plus the new next generation NS3/4A protease inhibitor GS-9857 for 8 weeks was effective, achieving SVR12 rates over 95% across different patient populations including previously difficult-to-treat patients with cirrhosis, genotype 3 HCV infection and previous nonresponse to treatment. This regimen which was safe and well tolerated, with no specific toxicity signal observed in this first clinical study with GS-9857.

This study explored whether durations less than 8 weeks could be effective when three potent antivirals with different mechanisms of action are used in combination. Although 6 weeks duration of SOF/VEL plus GS-9857 achieved SVR rate >90% in treatment-naïve genotype 1 patients without cirrhosis, results in more difficult-to-treat patients with cirrhosis and DAA-experienced patients were suboptimal. Shortening duration to only 4 weeks in the treatment-naïve genotype 1 patients without cirrhosis reduced SVR to 27%, which is similar to the results reported from 3 other recent studies of 3 or 4 DAAs for 4 weeks in this patient population (E Lawitz et al, J Hepatol 62:O006, Abstract; M Sulkowski et al, Hepatology 62:702, Abstract).[10] These results suggest that 8 weeks is the threshold of treatment duration with combination DAAs for the easier-to-treat patient population, not 4 or 6 weeks as suggested by recent viral kinetic models.[11,12] This discrepancy may be explained by the stability of the HCV replication complex. Future attempts to shorten duration of DAA regimens to less than 8 weeks will probably require the addition of a host-targeting agent

such as RG-101, an miR-122 antagonist, which has been shown to do so in the interim results of an ongoing phase 2 study (Horvath G et al, J Hepatol 64:GS08).

This single 8 week RBV-free single tablet regimen for the DAA-naïve patient population could remove the need for most pre-treatment assessments and simplify treatment algorithms. The excellent tolerability and lack of on-treatment monitoring would make this regimen ideal for community prescribing, which could significantly enhance treatment uptake. If combined with enhanced public awareness and community-based targeted testing, such "one size fits all" regimens may significantly accelerate current HCV elimination programs.

The earliest interferon-free regimens were discontinued because of high rates of virologic failure (VX-222 and telaprevir (Di Bisceglie A et al. J Hepatol 54:S540); daclatasvir and asunaprevir; faldaprevir and deleobuvir; mericitabine and danoprevir; mericitabine and danoprevir and setrobuvir; tegobuvir and vedroprevir and ledipasvir).[13-17] These regimens consisted of two or more DAAs with low barriers to resistance and were associated with rapid selection of NS3, NS5A or NS5B RASs leading to both on-treatment breakthrough and post-treatment relapse, often with dual or triple DAA resistance. Although the currently approved DAA regimens (ledipasvir/sofosbuvir, daclatasvir and sofosbuvir, simeprevir and sofosbuvir, paritaprevir/ombitasvir and dasabuvir; elbasvuir/grazoprevir) have a higher barrier to resistance and low rates of virologic failure, most relapsers have persistent RASs, which limit retreatment options.

In contrast to these earlier generation DAAs, sofosbuvir, velpatasvir, and GS-9857 exhibit potent antiviral activity against all HCV genotypes. In addition, GS-9857 and velpatasvir retain potent activity in the presence of most commonly detected NS3 and NS5A RASs, respectively. Baseline RASs, including Y93H, the only NS5A substitution which confers high-level resistance to velpatasvir, did not appear to affect response to short durations of treatment with sofosbuvir/velpatasvir plus GS-9857, suggesting a very high barrier to resistance of this regimen. Of note, patients with multiple RASs at baseline achieved SVR when treated with the study

regimen (including one patient with both NS5A and NS5B RASs and one patient with NS3/4A, NS5A and NS5B RAS(s). The resistance characteristics of this regimen suggests a great potential for its use as a salvage therapy for DAA-experienced patients, where RASs may emerge or be enriched at the time of failure. However, the numbers of patients with prior DAA experience in our study is not sufficiently large for any definitive conclusions to be made concerning the efficacy of this regimen in patients who did not achieve SVR after treatment with an NS5A inhibitor. The short 6-week treatment duration in the current study in a group of patients who previously failed two classes of DAA led to a SVR of 66%, and a 12-week treatment duration of SOF/VEL plus GS-9857 is being studied in other Phase 2 studies for this population.

The rate of virologic failure in the different groups evaluated in this study was clearly related to duration of therapy: 73% after 4 weeks of treatment, 19% after 6 weeks of treatment and 4% after 8 weeks. Only two patients had a treatment-emergent RAS at the time of virologic failure, further confirming the high barrier to resistance of this regimen and suggesting its potential as a salvage regimen for DAA-experienced patient with longer treatment duration. SOF/VEL/GS-9857 is now coformulated as a single tablet which is being evaluated in the larger Phase III programme, which includes different patient populations, including DAA-experienced patients. This group of DAA-experienced patients is growing and currently represents an unmet medical need.

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Author names in bold designate shared co-first authors.

Table 1. Demographics and Baseline Characteristics

	Genotype 1						Genotype 3		
	Treatment naïve, no cirrhosis 4 weeks (n=15)	Treatment naïve, no cirrhosis 6 weeks (n=15)	Treatment naïve with cirrhosis 6 weeks (n=15)	DAA-experienced ± cirrhosis 6 weeks (n=30)	PEG+RBV-experienced with cirrhosis 8 weeks (n=17)	PI-experienced ± cirrhosis 8 weeks (n=28)	Treatment naïve with cirrhosis 6 weeks (n=18)	PEG+RBV-experienced with cirrhosis 8 weeks (n=19)	DAA-experienced ± cirrhosis 8 weeks (n=4)
Mean age, years (range)	54 (40, 64)	50 (24, 65)	59 (51, 66)	55 (35, 73)	58 (48, 70)	57 (39, 66)	52 (39, 64)	55 (44, 66)	56 (43, 62)
Patient sex, n (%)									
Male	9 (60)	7 (47)	11 (73)	24 (80)	14 (82)	19 (68)	10 (56)	15 (79)	4 (100)
Female	6 (40)	8 (53)	4 (27)	6 (20)	3 (18)	9 (32)	8 (44)	4 (21)	0
Race									
White	12 (80)	14 (93)	14 (93)	27 (90)	16 (94)	24 (86)	12 (67)	18 (95)	3 (75)
Asian	2 (13)	1 (7)	0	1 (3)	0	2 (7)	0	0	0
Pacific Islander	1 (7)	0	1 (7)	2 (7)	1 (6)	1 (4)	3 (17)	1 (5)	0
Maori	0	0	0	0	0	1 (4)	3 (17)	0	1 (25)
Other	0	0	0	0	0	1 (4)	3 (17)	0	1 (25)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.3 (0.5)	6.0 (0.7)	6.0 (0.9)	6.3 (0.5)	6.3 (0.5)	6.1 (0.6)	6.1 (0.7)	6.3 (0.4)	6.9 (0.2)
Genotype, n (%)									
1a	11 (73)	11 (73)	14 (93)	23 (77)	15 (88)	24 (86)	--	--	--
1b	4 (27)	4 (27)	1 (7)	7 (23)	2 (12)	4 (14)	--	--	--
3	--	--	--	--	--	--	18 (100)	19 (100)	4 (100)
Mean BMI, kg/m^2 (range)	27 (20, 33)	25 (21, 32)	27 (20, 39)	27 (20, 40)	30 (22, 45)	28 (19, 40)	29 (20, 41)	27 (21, 33)	28 (24, 31)
Mean Platelet Count, 10^3/mL	220	216	134	217	160	191	162	121	168
IL28B genotype, n (%)									
CC	5 (33)	5 (33)	8 (53)	6 (20)	6 (35)	4 (14)	10 (56)	8 (42)	3 (75)
CT	10 (67)	8 (53)	7 (47)	18 (60)	9 (53)	21 (75)	6 (33)	9 (47)	1 (25)
TT	0	2 (13)	0	6 (20)	2 (12)	3 (11)	2 (11)	2 (11)	0
Cirrhosis	0	0	15 (100)	5 (17)	17 (100)	11 (39)	18 (100)	19 (100)	2 (50)

Table 2. Efficacy

	Genotype 1						Genotype 3		
	Treatment naïve, no cirrhosis 4 weeks (n=15)	Treatment naïve, no cirrhosis 6 weeks (n=15)	Treatment naïve with cirrhosis 6 weeks (n=15)	DAA-experienced ± cirrhosis 6 weeks (n=30)	PEG+RBV-experienced with cirrhosis 8 weeks (n=17)	PI-experienced ± cirrhosis 8 weeks (n=28)	Treatment naïve with cirrhosis 6 weeks (n=18)	PEG+RBV-experienced with cirrhosis 8 weeks (n=19)	DAA-experienced ± cirrhosis 8 weeks (n=4)
During treatment									
Week 2	8 (53)	10 (67)	10 (67)	13 (43)	7 (41)	17 (61)	16 (89)	8 (42)	1 (25)
Week 4	15 (100)	15 (100)	15 (100)	28 (93)	13 (76)	24 (86)	18 (100)	16 (84)	4 (100)
Week 8	--	15 (100)	15 (100)	29 (97)	17 (100)	27 (96)	18 (100)	18 (95)	4 (100)
After treatment									
Week 4	11 (73)	15 (100)	13 (87)	26 (87)	17 (100)	26 (93)	16 (89)	19 (100)	4 (100)
Week 12 (SVR)	**4 (27)**	**14 (93)**	**13 (87)**	**20 (67)**	**17 (100)**	**25 (89)**	**15 (83)**	**19 (100)**	**4 (100)**
95% CI	8 to 55	68 to >99	60 to 98	47 to 83	81 to 100	72 to 98	59 to 96	82 to 100	40 to 100
Virologic failure									
Breakthrough	0	0	0	0	0	0	0	0	0
Relapse	11 (73)	1 (7)	2 (13)	10 (30)*	0	3 (11)	2 (11)	0	0
Lost to follow-up	0	0	0	0	0	0	1 (6)	0	0

*One of these patients, a 61-year-old male Pacific Islander, had progressively lower levels of HCV RNA at every treatment visit, but did not achieve HCV RNA <LLOQ until post-treatment week 2; he had relapsed by post-treatment week 4.

Table 3. Adverse events, discontinuations due to adverse events, and laboratory abnormalities

	Genotype 1						Genotype 3		
	Treatment naïve, no cirrhosis 4 weeks (n=15)	Treatment naïve, no cirrhosis 6 weeks (n=15)	Treatment naïve with cirrhosis 6 weeks (n=15)	DAA-experienced ± cirrhosis 6 weeks (n=30)	PEG+RBV-experienced with cirrhosis 8 weeks (n=17)	PI-experienced ± cirrhosis 8 weeks (n=28)	Treatment naïve with cirrhosis 6 weeks (n=18)	PEG+RBV-experienced with cirrhosis 8 weeks (n=19)	DAA-experienced ± cirrhosis 8 weeks (n=4)
Patients with ≥1 AE	13 (87)	12 (80)	10 (67)	23 (77)	15 (88)	22 (79)	15 (83)	15 (79)	3 (75)
Patients with serious AE	0	0	0	0	0	1 (4)	0	2 (11)	0
Patients who discontinued treatment due to AE	0	0	0	0	0	0	0	0	0
Adverse events occurring in ≥5% of patients									
Headache	2 (13)	6 (40)	4 (27)	6 (20)	3 (18)	5 (18)	6 (33)	4 (21)	1 (25)
Nausea	5 (33)	5 (33)	3 (20)	5 (17)	1 (6)	3 (11)	3 (17)	7 (37)	1 (25)
Fatigue	2 (1)	5 (33)	2 (13)	3 (10)	3 (18)	7 (25)	3 (17)	2 (11)	1 (25)
Diarrhoea	2 (13)	3 (2)	0	2 (7)	1 (6)	6 (21)	4 (22)	0	2 (50)
Upper respiratory tract infection	2 (13)	0	0	1 (3)	0	4 (14)	4 (22)	1 (5)	1 (25)
Vomiting	1 (7)	1 (7)	0	0	1 (6)	1 (4)	2 (11)	3 (16)	0
Grade 3/4 laboratory abnormalities									
Neutrophils .50 to .75 GI/L	0	0	1 (7)	0	0	0	0	1 (5)	0
Platelets 25 to <50 mm^3	0	0	0	0	1 (6)	0	1 (6)	0	0
WBC 1.00 to <1.50 mm^3	0	0	1 (7)	0	0	0	0	0	0
AST >5 to 10 × ULN	0	0	0	1 (3)	1 (6)	0	0	0	0
Creatine Kinase ≥20 × ULN	0	0	0	1 (3)	0	0	0	0	0
Lipase >3 to 5 × ULN	0	0	1 (7)	2 (7)	0	1 (5)	1 (6)	1 (5)	0
Lipase >5 × ULN	0	0	0	1 (3)	0	0	0	0	0
Serum glucose 3	0	0	1 (7)	0	0	1 (5)	0	3 (16)	1 (25)

Data are n (%). AE, adverse event

Figure 1. Patient disposition