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Retreatment with Elbasvir, Grazoprevir, Sofosbuvir +/- Ribavirin is effective for GT3 and GT1/4/6 HCV infection after relapse

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ABBREVIATIONS:

DAA – direct acting antiviral

HCV – hepatitis C Virus

RAS – resistance-associated substitutions

SOF – sofosbuvir

ELB – elbasvir

GZR – grazoprevir

RBV – ribavirin

GT – genotype

NS5A – non-structural protein 5A

SVR12 – sustained virological response week 12

RNA – ribonucleic acid

EOT – end of treatment

MELD – model for end stage liver disease

INR – international normalised ratio

HCC – hepatocellular carcinoma

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LAY SUMMARY: A small number of patients are not cured after their first course of hepatitis C treatment. Retreatment of these patients should include a combination of drugs to treat resistant hepatitis C virus. The combination of sofosbuvir, elbasvir, grazoprevir and ribavirin appears to be effective for retreatment of these patients, including for genotype 3 for which some of these drugs are less effective when used alone. In this study, there was a high rate of cure and treatment overall was safe. This combination could provide an alternate retreatment strategy in carefully selected settings.

KEY WORDS: hepatitis C, virological relapse, resistance associated substitution, salvage, retreatment

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Abstract:

Introduction:

Despite highly effective direct-acting antiviral (DAA) therapies for chronic hepatitis C virus (HCV) infection, some patients experience virological relapse. Salvage regimens should include multiple agents to suppress emergence of resistance-associated substitutions (RAS) and minimise treatment failure. The combination of sofosbuvir (SOF) and elbasvir/grazoprevir (ELB/GZR) ±ribavirin (RBV) is an effective retreatment strategy for HCV genotype (GT)1 and 4 infection. We hypothesized that SOF and ELB/GZR (±RBV) would also be an effective salvage regimen for DAA-experienced GT3 patients.

Methods:

We evaluated the efficacy and safety of SOF/ELB/GZR±RBV in DAA-experienced participants with chronic HCV infection who had prior relapse. Participants were treated at four hospitals between December 2016 and March 2018 for either 12- or 16-weeks. The primary endpoint was sustained virological response at week 12 post-treatment (SVR12) using intention-to-treat analysis.

Results:

There were 40 participants included in the analysis. The mean age was 53 years, 53% had GT3, 33% had GT1 infection, and 63% had cirrhosis. Fifty-eight percent were treated for 12 weeks, 42% were treated for 16 weeks, and 90% received RBV. The SVR12 rate was 98% overall, 100% in non-GT3 participants and 95% in GT3 participants. One GT3 cirrhotic participant relapsed. ELB/GZR was stopped at week 6 in one GT3 cirrhotic participant who switched to SOF/velpatasvir/RBV for a further 12 weeks and achieved SVR12. RBV dose reduction was required in two participants. Treatment was otherwise well tolerated.

Discussion:

The combination of SOF/ELB/GZR±RBV is effective and safe for difficult-to-cure patients who relapse after first-line DAA, including those with cirrhosis and GT3 infection.

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Introduction:

The introduction of highly effective and well tolerated direct acting antiviral (DAA) therapy has revolutionised hepatitis C virus (HCV) treatment. Despite excellent cure rates which exceed 95%, some patients experience virological relapse after treatment. Virological relapse is associated with the selection of HCV resistance associated substitutions (RAS), which reduce viral susceptibility to

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currently available DAAs (1). NS5A inhibitors are the backbone of most DAA regimens and selection of NS5A RAS is the most common reason for DAA failure. NS5A variants can persist for many years post-relapse (2). Variants in the NS5B region and/or NS3/4a region may also be selected with sofosbuvir (SOF) or protease inhibitor therapy, respectively. The ideal salvage regimen should involve combination therapy with at least two agents that are active against all the prevalent HCV quasispecies. Triple combination therapy involving sofosbuvir (SOF), a protease inhibitor, and an NS5A inhibitor is therefore attractive as a salvage strategy.

Elbasvir (ELB) plus grazoprevir (GZR) is licenced for treatment of HCV genotype (GT)1 and 4 infection (3). Recent data have demonstrated that ELB/GZR in combination with SOF (± ribavirin (RBV)) is also an effective salvage treatment for cirrhotic DAA-experienced GT1/4 patients, those genotypes for which ELB/GZR has the greatest *in-vitro* and *in-vivo* activity (4). ELB and GZR alone have reduced effectiveness against HCV GT3 infection, with a significantly higher EC_{50} than for GT1 HCV *in vitro* and suboptimal SVR12 rates in clinical trials (3, 5). Despite this, ELB/GZR in combination with SOF plus RBV was highly effective for the treatment of DAA-naive GT3 patients; in a large prospective study SVR12 rates exceeded 94% in those treated for 12 to 16 weeks, including participants with cirrhosis (6).

In this context, we hypothesized that SOF plus ELB/GZR ± RBV (ELB/GZR/SOF±RBV) would be an effective salvage regimen for DAA experienced patients, irrespective of GT or underlying cirrhosis.

Patients and methods:

Patients:

From December 2016 a special access scheme supported by Merck, Sharp and Dohme Australia allowing access to ELB/GZR for use in combination with SOF/RBV for retreatment of patients who were non-responders to licensed DAA therapy. SOF/RBV were prescribed via the Pharmaceutical Benefit Scheme which reimburses the cost of HCV treatment for all Australians (7). Patients for whom this treatment was accessed from four tertiary centres in Melbourne, Australia were consecutively treated with SOF 400mg daily, fixed dose combination ELB/GZR 100mg/50mg daily, with or without RBV (600-1200mg daily) for either 12 or 16 weeks. Duration of therapy was decided on an individual basis by the treating clinician at each participating site.

Eligibility criteria for the special access scheme included non-response following treatment with an approved NS5A inhibitor containing DAA regimen, defined as detectable HCV RNA at week 12 post treatment, and infection with HCV GT 1, 3, 4 or 6. All participants in this study were deemed compliant with their initial DAA treatment regimen. Exclusion criteria for this study included:

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decompensated chronic liver disease (Child Pugh Category B/C), active or suspected hepatocellular carcinoma, contraindicated drug-drug interactions and prior liver transplantation. Cirrhosis was determined by liver stiffness measurements using FibroScan (cut-off ≥12.5kPa), prior liver biopsy or radiological and/or endoscopic evidence of portal hypertension. Portal hypertension was defined as the presence of oesophageal varices at endoscopy or splenomegaly, intra-abdominal varices or ascites identified on abdominal imaging.

Assessment:

All participants were reviewed at baseline, treatment week 4, end-of-treatment (EOT) and 12 weeks post-treatment at a minimum. On-treatment virological response was defined as undetectable HCV RNA on PCR testing. The primary outcome was SVR12, defined as undetectable HCV RNA at 12 weeks post-EOT. All cirrhotic patients were enrolled in hepatocellular carcinoma (HCC) surveillance.

The secondary outcomes were frequency of treatment and non-treatment related adverse events and the frequency of denovo or recurrent HCC. Safety and tolerability were monitored at each clinical review and further investigations were arranged where deemed appropriate. All adverse events, laboratory abnormalities and treatment interruptions and/or discontinuations were recorded.

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, Good Clinical Practice Guidelines, and regulatory requirements. The study was approved by the St Vincent's Hospital Melbourne Human Research Ethics committee prior to governance review at each participating hospital. A waiver of consent was granted by the St Vincent's Hospital HREC and then ratified at each participating site.

Assessment for NS5A resistance-associated substitutions:

A subset of participants were investigated for sequences encoding NS5A RAS at time of relapse, prior to treatment with the study regimen. Testing was performed at the Victorian Infectious Disease Reference Laboratory using Sanger sequencing with a prevalence threshold for detection of 20%.*Statistical Analysis:*

Results are presented as median with interquartile range for continuous data and number (percentage) for categorical data. Analysis was performed using Stata 15.2 for Windows, StataCorp LLC, USA.

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Results:

Participant characteristics:

Forty participants with chronic HCV infection and prior virological failure after HCV DAA therapy were included. Baseline characteristics are displayed in Table 1. The sample was predominately male (n=32, 90%), just over half had HCV GT3 infection (n=21, 53%) and majority were cirrhotic (n=25, 63%). Of those with cirrhosis, nine (36%) had portal hypertension.

Prior treatment regimens included SOF + ledipasvir (n=15, 37%), SOF + daclatasvir (n=22, 55%), SOF + velpatasvir (n=1, 3%), ELB/GZR (n=1, 3%) and paritaprevir/r + ombitasvir + dasabuvir (n=1, 3%). Treatment durations are detailed in Table 1. All participants had completed the entire course of the prior treatment and had detectable HCV RNA at 12 weeks post treatment completion. A mean duration of 10 months (range 5-19 months) had elapsed between EOT of the initial regimen and initiation of the study regimen. HCV NS5A sequencing results were available in 26/40 subjects, with the majority having NS5A RAS detectable (Supplementary Table 1).

HCV DAA therapy and virological response:

Of the 40 participants, 23 (58%) and 17 (42%) were treated with 12 weeks and 16 weeks of SOF/ELB/GZR±RBV respectively. Thirty-six (90%) received RBV; RBV was omitted in one GT3 participant with a history of prior RBV intolerance, and in three GT1/6 participants at the discretion of the treating physician due to concerns about tolerance. Treatment outcomes are displayed in Figure 1. Overall, the SVR rate was 97.5% (n=39/40). The SVR rate amongst HCV GT1, 4 and 6 participants was 100% (n=19/19), irrespective of treatment duration (12 or 16 weeks) or inclusion of RBV. Amongst HCV GT3 participants, overall SVR rate was 95% (n=20/21), 90% (9/10) for 12 weeks of therapy and 100% (10/10) for 16 weeks. This included an SVR12 rate of 100% (5/5) in non-cirrhotic GT3 participants, and 94% (n=15/16) among cirrhotic GT3 participants.

One episode of virological relapse occurred in a HCV GT3 cirrhotic participant (Child Pugh A5, MELD 6), . NS5A RAS testing at relapse was significant for the Y93H RAS. The participant was treated with 12 weeks of SOF/ELB/GZR/RBV, but had detectable HCV RNA at SVR12 time point. A second HCV GT3 cirrhotic participant with portal hypertension (Child Pugh A6,, MELD 9) prescribed ELB/GZR/SOF/RBV for 16 weeks experienced an increase in bilirubin (30 to 50umol/L) and INR (1.3 to 1.5) at treatment-week 6, and was immediately switched to SOF + velpatasvir + RBV for an additional 12 weeks. Bilirubin remained stable at 40-50umol/L for the duration of RBV therapy before returning to

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baseline. The INR remained stable between 1.4 - 1.5 throughout the period of evaluation. There was no rise in the ALT or clinical decompensation event at any time. The participant went on to achieve SVR12.

One participant was commenced on ELB/GZR/SOF/RBV beyond the inclusion criteria of the ELB/GZR special access program. The participant was Child Pugh B7 at baseline), however the baseline hypoalbuminaemia (albumin 27g/L) was thought secondaryto diabetic nephropathy and significant proteinuria. There was no adverse event, and the participant achieved SVR12.

SVR12 rate was 100% (n=9/9) amongst participants with no HCV NS5A RAS and 94% (n=16/17) in participants with an NS5A RAS detected at baseline. SVR12 was achieved in 92% (n=12/13) of participants with virus with the Y93H/D/S NS5A RAS at baseline.

Hepatocellular carcinoma:

No *de novo* or recurrent hepatocellular carcinomas (HCC) were identified during the period of evaluation.

Adverse events:

Adverse events are detailed in Table 2. One HCV GT3 cirrhotic participant discontinued therapy at treatment week 6 as described. There were 25 adverse events in 19 participants. Most were RBV-related haematological abnormalities, but also included fatigue, headache, gastrointestinal upset, insomnia and rash and were mild in severity. Two participants required dose reduction of RBV for management of anaemia.

Discussion:

Whilst DAA therapy cures most people with HCV, a subset of patients do not respond to first line treatment. This hard-to-cure group is characterized by a high prevalence of HCV GT3 infection, cirrhosis, and portal hypertension (8). Our data suggests that the combination of SOF/ELB/GZR±RBV is highly effective for the retreatment of DAA non-responders, in both GT3 and GT1/4/6 HCV infection. The overall SVR12 rate was 98%, and 95% amongst GT3 cirrhotic participants, similar to approved pan-genotypic salvage regimens (9, 10).

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A small study has previously reported the efficacy of this regimen for the treatment of non-responders with GT 1/4 HCV infection (4) and the SVR12 rate was 100% (per protocol) in 25 patients. Our study is the first description of efficacy among a group of non-responders that included with patients with GT3 HCV infection who had relapsed after treatment with an NS5A containing regimen. In our study, 38/40 patients (21 who were GT3) had relapsed following treatment with a regimen including SOF plus an NS5A inhibitor. Both ELB and GZR have an EC_{50} for GT3 that is at least 10-fold greater than for GT1 (3). In clinical trials of treatment naïve patients, SVR12 rates were only 41% for HCV GT3 infected patients treated with ELB/GZR for 12 weeks (5). In contrast, combination therapy with SOF/ELB/GZR±RBV has been shown to be effective for treatment naïve patients with GT3 HCV, including patients with cirrhosis (6), with SVR12 rates > 90%. We now show a similar rate of SVR12 in treatment experienced patients. Our data support synergy between SOF and ELB/GZR and effectiveness for HCV GT3. Of note, the rate of SVR12 in our cohort is numerically higher than that reported in a cohort of participants (including HCV GT1, GT2 and GT3 infection) who were re-treated with SOF/velpatasvir/RBV for 24 weeks following relapse after a first course of SOF/velpatasvir (n=63/69, 91%) (11).

There was one episode of virological relapse in a HCV GT3 participant. The participant had previously relapsed following treatment with pegylated interferon and ribavirin and subsequently SOF/daclatasvir for 24 weeks, was cirrhotic and had virus with the Y93H NS5A RAS detectable at retreatment baseline which is associated with high level resistance to NS5A inhibitors (12). The participant reported good adherence to 12 weeks of SOF/ELB/GZR/RBV600 before relapsing. It is possible that longer treatment duration for 16 weeks may have been more effective.

Combination SOF/ELB/GZR/RBV was safe. The most frequent adverse events were haematological abnormalities associated with RBV. A dose reduction was only required in two cases. The most serious adverse event occurred in a HCV GT3 participant with advanced cirrhosis. At TW6 the participant's bilirubin level had risen from 30 to 50umol/L and INR from 1.3 to 1.5. The participant was switched to SOF/velpatasvir/RBV due to concern about protease inhibitor related hepatotoxicity. The participant's hyperbilirubinaemia at TW6 may be attributable to RBV-associated haemolysis, however this does not account for their INR prolongation. HCV NS3/4A protease inhibitors are contraindicated in Child Pugh B/C cirrhosis, in whom accumulation may cause hepatotoxicity, and participant with Child Pugh A cirrhosis should be closely monitored. Notably, the participant went on to achieve SVR12, suggesting that 6 weeks of protease inhibitor exposure, with a longer tail of SOF/velpatasvir/RBV was sufficient to eradicate virus.

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Following the introduction of HCV DAAs, there was concern regarding potential increases in HCC incidence and recurrence with antiviral therapy (14). More recent data suggests this correlation is unlikely (15). In the *Revenge* study, a comparable population with HCV GT1/4 infection was treated with SOF/ELB/GZR/RBV, in which 19% (5/26) of the participants developed HCCs during the period of evaluation (4). The authors attributed this to the study populations advanced age, duration of HCV infection and high prevalence of cirrhosis, rather than to the study regimen. This is supported by our data where no recurrent or *de novo* HCCs were identified during the period of evaluation.

Two DAA regimens have recently been approved by the Federal Drug Administration and European Medicines Agency for the treatment of DAA non-responders. These include the combination of SOF/velpatasvir/voxilaprevir, approved for the treatment of all HCV genotypes, and glecaprevir/pibrentasvir, approved for retreatment of people with GT1 HCV previously treated with a regimen including either (but not both) an NS5A inhibitor or an NS3/4A protease inhibitor; and non-GT1 HCV who have previously been treated with SOF/PR. Whilst these regimens are licensed in the US and some countries in Western Europe, they are not yet available in all regions due to licencing or funding restrictions. Our data supports the combination of SOF/ELB/GZR±RBV as a second pan-genotypic re-treatment option, combining drugs which are currently licensed and available in most regions. The role of the different re-treatment options is likely to vary between regions according to cost and drug availability.

Study limitations include an inability to define the optimal duration for SOF/ELB/GZR±RBV and the role of RBV, particularly for HCV GT3 participants, for which prospective randomised studies are required. Until such time, we recommend treating GT3 infected patients for 16 weeks in combination with RBV, where possible.

In conclusion, the combination of SOF/ELB/GZR±RBV was safe and effective salvage treatment for patients who had not responded to a previous NS5A-contiaining DAA therapy. It was effective for the treatment of hard-to-cure GT3 as well as GT1/4/6 HCV infection. The DAAs in this regimen are currently available in many regions, and represent another option for treating patients who do not respond to a first course of DAA therapy, with the aim of stopping the progression of liver disease and reducing HCV-related morbidity and mortality.

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References:

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1. Pawlotsky J-M. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;151(1):70-86.

2. Wyles D, Mangia A, Cheng W, et al. Long-term persistence of HCV NS5A resistance associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir. Antivir Ther. 2017;23:229-38.

3. Therapeutic Goods Administration. Product Information, Zepatier [Accessed at: https://www.tga.gov.au/sites/default/files/auspar-grazoprevir-170515-pi.pdf on 15th September, 2018.

4. De Ledinghen V, Laforest C, Hézode C, et al. Retreatment with sofosbuvir plus grazoprevir/elbasvir plus ribavirin of patients with hepatitis C virus genotype 1 or 4 who previously failed an NS5A-or NS3-containing regimen: the ANRS HC34 REVENGE study. Clin Infect Dis. 2017;66(7):1013-8.

5. Gane E, Nahass R, Luketic V, et al. Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naïve, noncirrhotic HCV genotype 3-infected patients. J Viral Hepat. 2017;24(10):895-9.

6. Foster GR, Agarwal K, Cramp ME, et al. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. Hepatology. 2018;67(6):2113-26.

7. Pharmaceutical Benefit Scheme; Australian Government. 'General Statement for Drugs for the Treatment of Hepatitis C' accessed online on 6th December at http://www.pbs.gov.au/healthpro/explanatory-notes/general-statement-pdf/general-statement-hepatitis-cpdf. 2018.

8. Werner CR, Schwarz JM, Egetemeyr DP, et al. Second-generation direct-acting-antiviral hepatitis C virus treatment: Efficacy, safety, and predictors of SVR12. World J Gastroenterol. 2016;22(35):8050.

9. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376(22):2134-46.

10. Bourlière M, Gordon SC, Ramji A, et al. Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks as a salvage regimen in NS5A inhibitor-experienced patients with genotype 1-6 infection: the phase 3 POLARIS-1 study. Hepatology. 2016;64(Suppl 1):102A-3A.

11. Gane E, Shiffman M, Etzkorn K, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen, Hepatology. 2017 Oct;66(4):1083-1089.

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12. Lawitz EJ, Dvory-Sobol H, Doehle B, et al. Clinical resistance to velpatasvir (GS-5816), a novel pan-genotypic inhibitor of the hepatitis C virus NS5A protein. Antimicrob Agents Chemother. 2016 Aus;60(9)”5368-78.

13. Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018.

14. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65(4):727-33.

15. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol. 2017;67(6):1204-12.

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Table 1 – Baseline Characteristics

Baseline Characteristics	**N = 40**
Age, mean, [IQR]	53 [46-60]
Male gender, n (%)	32 (80%)
ALT U/L, median, [IQR]	87 [51-124]
HCV RNA IU/mL, median, [IQR][#]	1,842,281 [303,500-7,548,579]
Platelet count, median, [IQR]	188 [155-237]
Albumin, median, [IQR]	39 [36-40]
Bilirubin, median, [IQR]	15 [12-24]
INR, median, [IQR]	1.1 [1.0-1.1]
HCV Genotype, n (%)	
- 1a	11 (28%)
- 1b	2 (5%)
- 3[*]	21 (53%)
- 4[~]	3 (7%)

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- 6	3 (7%)
PR treatment experienced, n (%)	12 (30%)
Prior HCC, n (%)	2 (5%)
Active HCC, n (%)	0 (0%)
Liver stiffness measurements of non-cirrhotic participants, n	
- <6 kPa	7/15
- 6-9.5 kPa	7/15
- 9.5-12.5kPa	1/15
Cirrhotic, n (%)	25 (63%)
Child Pugh score	
- A5	18/25
- A6	6/25
- B7[+]	1/25
MELD score, mean [IQR]	8 [7-10]
Portal hypertension, n, (%)	9/25 (36%)
Prior HCV treatments	
- Sofosbuvir / Ledipasvir	15
- Sofosbuvir / Daclatasvir	22
- Sofosbuvir / Velpatasvir	1
- Elbasvir / Grazoprevir	1
- Paritaprevir/r, Ombitasvir, Dasabuvir	1
Duration of prior treatment	
- 8 weeks	2
- 12 weeks	20
- 24 weeks	18

Abbreviations: IQR, interquartile range, ALT, alanine aminotransferase, HCV, hepatitis C virus, RNA, ribonucleic acid, INR, international normalised ratio, PR, Pegylated interferon and ribavirin, HCC, hepatocellular carcinoma, MELD, model for end stage liver disease

[#] Median and interquartile rangepresented for 30/40 participants. 10/40 participants were HCV PCR positive at baseline, however quantitative HCV viral load testing was not performed.

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*GT subtyping was performed on 17/21 GT3 participants, all who were subtype 3a.

~ GT subtyping was performed on 2/3 GT$ participants, who were both subtype 4h.

Adverse events, n (%)	**N=25**
Haemoglobin decline	
20-40g/L	9 (23)
>40g/L	2 (5)
Requiring RBV dose reduction	2 (5)
Fatigue	5 (13)
Headaches	3 (8)
Gastrointestinal upset	3 (8)
Insomnia	1 (3)
Rash	1 (3)
Treatment discontinuation	1 (3)

[+]One Child Pugh B7 participant was commenced on the study regimen beyond the inclusion criteria of the special access scheme for ELB/GZR however baseline hypoalbuminaemia was attributed to poorly controlled type 2 diabetes with documented proteinuria

Table 2 – Adverse events

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Figure 1

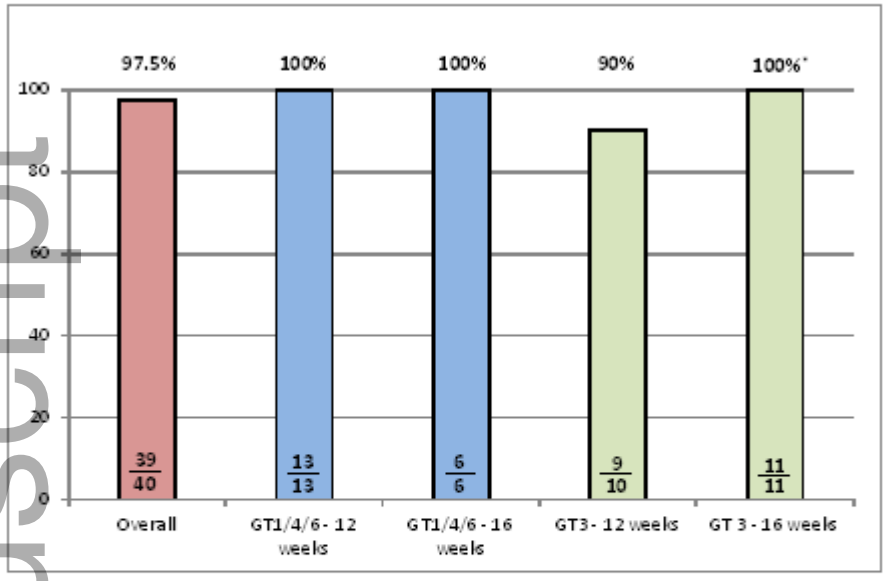

Figure 1: SVR12 rates by HCV genotype and duration of therapy

Abbreviations: GT, genotype

*One participant stopped SOF/ELB/GZR/RBV at TW6 due to increasing bilirubin and INR, was immediately changed to SOF/VEL/RBV for an addition 12 weeks and achieved SVR12.

~36/40 participants received ribavirin, which was omitted in two GT1, one GT6 and one GT3 participant

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