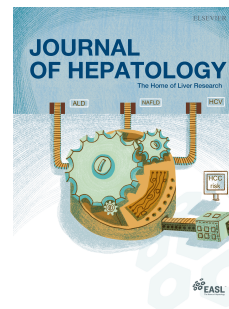


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Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection

Gail V. Matthews, Sanjay Bhagani, Marc Van der Valk, Juergen Rockstroh, Jordan J. Feld, Andri Rauch, Christine Thurnheer, Julie Bruneau, Arthur Kim, Margaret Hellard, David Shaw, Ed Gane, Mark Nelson, Patrick Ingiliz, Tanya L. Applegate, Jason Grebely, Phillipa Marks, Marianne Martinello, Kathy Petoumenos, Gregory J. Dore, on behalf of the REACT study group, Protocol Steering Committee, Marc van der Valk, Margaret Hellard, Ed Gane, Andri Rauch, Julie Bruneau, Arthur Kim, Sanjay Bhagani, Greg Dore, Pip Marks, Gail Matthews, Jason Grebely, Kathy Petoumenos, Marianne Martinello, Tanya Applegate, Jordan Feld, Jürgen Rockstroh, Coordinating Centre, Site Principal Investigators

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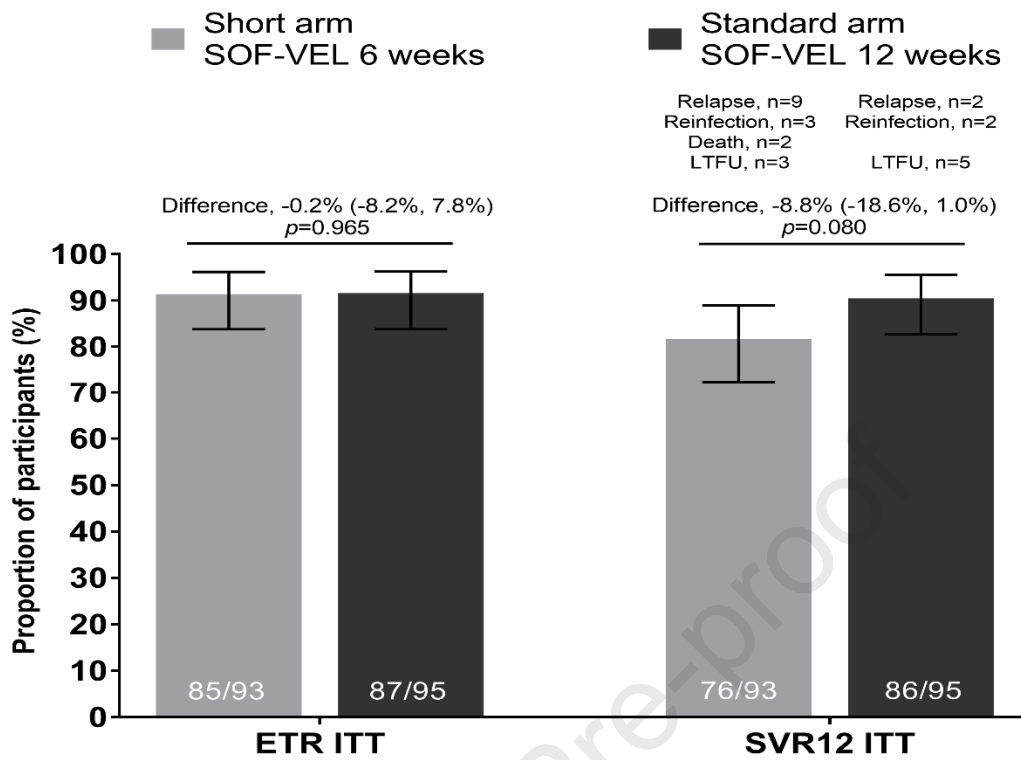
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Graphical abstract: End of treatment and SVR12 outcomes by intent-to-treat (ITT) analysis



Sorobuvir/velpatasvir 101-12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection

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GVM: grants from Gilead Sciences and AbbVie Inc, outside the submitted work;

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MvDW: grants and personal fees from AbbVie, grants and personal fees from Gilead, grants and personal fees from Johnson & Johnson, grants and personal fees from MSD, grants and personal fees from ViiV, outside the submitted work;

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Authors' Contributions:

GVM and GJD designed and proposed the study, with study design contributions from SB, MVdV, JR, JF, AR, JB, AK, MH, EG, TA, JG, KP

GVM, GD, SB, MVdV, JR, JF, AR, CT, JB, AK, MH, EG, MR, PI were involved in participant recruitment and data collection.

GVM, GD, SB, MVdV, JR, JF, AR, JB, AK, MH, EG, TA, JG, MM, PM, KP provided study governance through the Protocol Steering Committee.

RF conducted the data analyses, with oversight from MM and GVM.

GVM, MM and GJD drafted the manuscript, with input from all authors. All authors have seen and approved the final version of the manuscript.

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Lay summary

In this randomised trial one hundred and eighty people with recently acquired hepatitis C infection were randomly assigned to treatment using either a short 6-week course (93 people) or standard 12-week course (95 people) of the hepatitis C treatment sofosbuvir/velpatasvir. There were nine cases of relapse after treatment in the short course and two using the standard course. A shortened course of 6 weeks therapy for hepatitis C infection was considered not as effective as a standard twelve week course in people with recently acquired hepatitis C infection.

Data availability statement

Due to the sensitive nature of some of the data, including that related to injecting drug use, data included in this manuscript has not been placed in an open access database. However, data is available to be shared on request to the protocol steering committee.

Abstract

Background and aims: Shortened duration therapy for acute and recent hepatitis C virus (HCV) infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral regimens, however large randomised studies are lacking.

Methods: REACT was an NIH-funded multicentre international, open-label, randomised, phase 4 non-inferiority trial examining the efficacy of short course (6 weeks) versus standard course (12 weeks) therapy with sofosbuvir-velpatasvir for recent HCV infection (estimated duration of infection \leq 12 months). Randomisation occurred at week 6. The primary endpoint was SVR12 in the intention-to treat (ITT) population. A total of 250 participants were planned for enrolment. On advice of the data safety and monitoring board the study was halted early.

Results: Primary analysis population consisted of 188 randomised participants at termination of study enrolment; short arm (n=93), standard arm (n=95). Ninety seven percent were male and 69% HIV positive. ITT SVR12 was 76/93, 81.7% (95% CI 72.4-89.0) in the short arm and 86/95, 90.5% (95% CI 82.7-95.6) in the standard arm. The difference between the arms was -8.8 (95% CI: -18.6, 1.0). By modified ITT analysis in which non-virological reasons for failure were excluded (death, reinfection, lost to follow-up) SVR12 was 76/85, 89.4% (95% CI 80.8-95.0) in the short arm and 86/88, 97.7% in the standard arm (95% CI 92.0-99.7; difference -8.3%, p=0.025).

Conclusions: In this randomised study in recent HCV infection, 6 weeks sofosbuvir-velpatasvir did not meet the criteria for non-inferiority to standard 12 weeks duration.

Word count 243 words

INTRODUCTION

Individuals identified in the ‘acute’ phase of hepatitis C virus (HCV) infection have historically responded better to therapy than individuals with chronic HCV infection. Several studies in the interferon based-therapy era confirmed that duration of therapy, if commenced early, could be shortened by as much as half, with equivalent or higher sustained virological response (SVR) or ‘cure’. (1-3) This was demonstrated irrespective of whether the infection was considered acute (within the prior six months) or recent (within the prior one year) at therapy commencement (4), and was true across at-risk populations including people who inject drugs (PWID)(5) and people with HIV. (6, 7)

With the advent of direct acting antiviral (DAA) therapies, the paradigm of shortened treatment for those with acute or recent HCV infection has been further examined. Although studies with initial regimens (including sofosbuvir and ribavirin) were disappointing, (8, 9) several single arm studies with more potent regimens demonstrated encouraging results. (10-12) One of the largest studies, the Dutch Acute HCV in HIV (DAHHS2) study, reported an SVR of 99% in 80 individuals with genotype 1 or 4 using a shortened duration of 8 weeks grazoprevir-elbasvir. (13) Most recently, the first pan-genotypic study in recent HCV infection (TARGET3D) demonstrated an SVR of 96% (per-protocol) in 30 individuals using six weeks of glecaprevir-pibrentasvir.(14) Although encouraging, these studies are limited by the lack of control group and small sample sizes, reflecting the difficulties of identifying and recruiting large numbers of individuals in early HCV infection.

Recruiting through a large international network, the Recently Acquired HCV Infection Trial (REACT) aimed to test the hypothesis that six weeks (short) of sofosbuvir-velpatasvir is non-inferior to 12 weeks (standard) of sofosbuvir-velpatasvir among people with recent HCV infection.

METHODS

Study design and randomisation

In this open-label international multicentre phase 3 trial, adults with recent HCV were randomly assigned (1:1) to receive sofosbuvir-velpatasvir 400mg-100mg once daily for six or 12 weeks. Randomisation was undertaken using permuted block design with computer random number generator using fixed block size of four, stratified according to site and HIV status, and occurred between week five and six on treatment. Block size was known only to the study statistician and clinical trial manager. Participation was capped for HCV/HIV coinfection enrolled to the study at 70% of the total study population, additionally, the number of participants with HCV reinfection enrolled to the study was originally capped at 20% of the total study population (although subsequently revised to uncapped). Participants randomised to the short arm completed therapy at the end of six weeks, whilst those in the standard arm continued for a further six weeks (total of 12 weeks).

Participants

Participants were screened and enrolled at 24 sites: Australia (n=5), Canada (n=4), Germany (n=4), Netherlands (n=1), New Zealand (n=1), Switzerland (n=3), United Kingdom (n=4), and United States (n=2). Study recruitment was conducted through a network of tertiary viral hepatitis clinics (n=18), and primary care clinics (n=6)

Adults (age ≥ 18 years) with recent HCV infection as defined below, (genotypes 1-6) and HCV RNA $\geq 10,000$ IU/mL at screening were eligible. Individuals with acute or chronic hepatitis B co-infection were excluded. Full eligibility criteria are provided in the study protocol, available in the *Supplementary Material*.

Sites were instructed to observe participants for four to 12 weeks between screening and baseline, providing an opportunity to assess for HCV spontaneous clearance. The timing of treatment initiation was made by the investigator on an individual basis at site level.

Study definitions

Recent primary HCV infection was defined as initial detection of anti-HCV antibody and/or HCV RNA within six months of enrolment and either: (i) documented recent HCV seroconversion (anti-HCV antibody negative result in the 18 months prior to enrolment) or (ii) acute clinical hepatitis (jaundice or alanine aminotransferase [ALT] greater than 10 times the upper limit of normal [ULN]) within the previous 12 months with the exclusion of other causes of acute hepatitis or (iii) acute asymptomatic hepatitis (acute rise in ALT $>5x$ ULN) within the previous 12 months with the exclusion of other causes of acute hepatitis. Recent HCV reinfection was defined as new detectable HCV RNA within six months of enrolment and evidence of prior spontaneous or treatment-induced clearance (previous positive anti-HCV antibody and undetectable HCV RNA on ≥ 2 occasions).

The presentation of recent HCV infection at the time of diagnosis was classified as either acute clinical or asymptomatic infection. Acute clinical infection included participants with a documented clinical history of symptomatic seroconversion illness (including, but not limited to, the presence of jaundice, nausea/vomiting, abdominal pain, fever and hepatomegaly) and those without clinical symptoms, but with a documented peak ALT greater than ten times ULN within the 12 months prior to diagnosis. Asymptomatic infection included participants with anti-HCV antibody seroconversion or reinfection, but no acute clinical symptoms or documented peak ALT less than ten times ULN.

In addition to these definitions of recent primary HCV and recent HCV reinfection, estimated duration of HCV infection less than 12 months at screening was required for inclusion. The estimated date of HCV infection in those with acute clinical infection was calculated as six weeks before the onset of seroconversion illness or six weeks before the first ALT greater than ten times ULN. The estimated date of HCV infection in those with asymptomatic infection was calculated as the midpoint between the last negative anti-HCV antibody or HCV RNA and the first positive anti-HCV antibody or HCV RNA. For participants who were anti-HCV antibody negative and HCV RNA positive at screening, the estimated date of infection was six weeks before enrolment, regardless of symptom status.

Virological definitions

HCV virological suppression was defined as HCV RNA below the lower limit of quantification (LLoQ). An end-of-treatment response (ETR) was defined as HCV RNA below the LLoQ (target not detected or target detected, not quantifiable) at the end of treatment (date of treatment cessation). SVR12 was defined as HCV RNA below the LLoQ at or after 12 weeks post cessation of treatment. Treatment failure was defined as either virologic failure (HCV RNA above the LLoQ at 12 weeks post cessation of treatment with reinfection excluded on sequencing) or non-virologic failure (including reinfection, death, premature treatment discontinuation, loss to follow up or missing HCV RNA values). Reinfection was defined as HCV RNA above the LLoQ after end of treatment with detection of infection with an HCV strain that was distinct from the primary infecting strain, confirmed as heterologous virus on sequencing. SVR12 assessment was nominally set at day 84 post treatment, with a lower limit of day 70 post-treatment.

Study assessments

In the short duration arm, scheduled study visits were undertaken at baseline, treatment weeks one, two, four and six (end of treatment), and post-treatment weeks four and 12. In the standard

duration arm, scheduled study visits were undertaken at treatment weeks one, two, four, six, eight, 10 and 12 (end of treatment), and post-treatment weeks four and 12. Randomisation occurred during week five on treatment (prior to the week six study visit). Study drug was dispensed at all scheduled visits (except week one) between baseline and end of treatment (14-day supply). Study drug adherence was assessed by pill count and self-reported adherence questionnaires at each scheduled visit between week two and end of treatment.

The presence of HCV RNA in plasma was assessed at all scheduled study visits using Aptima HCV Quant Dx assay, version 2.15.5 (LLoQ 10IU/mL; Hologic, Inc., Marlborough, MA, USA), with centralised testing performed at St Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia). Sequencing was conducted on HCV RNA extracted from plasma using published methods. Briefly, reverse transcription of HCV RNA was performed with random hexamers using the Invitrogen™ Superscript™ IV VILO™ Master Mix (ThermoFischer Scientific), and the Core-E2, NS5A and NS3 HCV regions were amplified by polymerase chain reaction.(15, 16) Sanger sequencing was performed at the Australian Genome Research Facility on the Applied Biosystems™ 3730xl DNA Analyzer. Sequence curation was performed using RECall.(17) The presence of polymorphisms in NS3 and NS5A at baseline (and at virological failure when occurring) was evaluated using Geno2PhenoHCV. (18)

Study endpoints

The primary endpoint was undetectable HCV RNA below the LLoQ at 12 weeks following the completion of sofosbuvir-velpatasvir treatment (SVR12). Secondary endpoints included treatment adherence, and treatment-emergent adverse events.

Statistical analysis and sample size

A total of 250 participants (1:1 randomisation) were planned for enrolment, randomisation and evaluation as the intention-to-treat (ITT) population. Given a sample size of 250 people, an assumption that the proportion achieving SVR12 would be 90% in the 12 week arm, and a lower confidence bound for an SVR12 difference (six week arm minus 12 week arm) greater than -12%, the study had approximately 80% power to demonstrate non-inferiority of the six week arm as compared to the 12 week arm. The non-inferiority margin of 12% was selected in accordance with the principles outlined in guidance on conducting non-inferiority trials (19) (20) with the choice of margin also taking into account the clinical significance of SVR12 in relation to stage of infection. A narrower non-inferiority margin would be justified in the setting of chronic HCV infection, particularly more advanced liver disease. In contrast, given that early intervention is being considered in the context of potential HCV treatment as prevention and elimination strategies, a broader margin was considered pragmatic and appropriate.

A Data Safety and Monitoring Board (DSMB) was established prior to trial commencement consisting of a blinded external statistician and three clinicians. An initial DSMB review was pre-determined for when the first 50 participants in each arm reached the SVR12 visit. At this review, the DSMB requested a further analysis after a total of 60 participants reached SVR4. Following this second review, recruitment was halted in May 2019 given concerns regarding efficacy in the six-week arm. Participants in screening or on treatment but prior to randomisation continued in the study and received 12 weeks of sofosbuvir and velpatasvir but were not randomised or included in the primary analysis population.

Primary efficacy and safety data were analysed in the ITT population (which included all randomized participants), with loss to follow-up deemed treatment failure. The modified intention-to-treat (mITT) population included participants in the ITT population, but excluded those with non-virological reasons for treatment failure (including death and loss to follow up)

and reinfection. The per-protocol (PP) population included participants who received $>90\%$ of scheduled treatment for $>90\%$ of the scheduled treatment period with follow-up virologic data at SVR12 (excluding reinfection and retreatments).

Categorical parameters were summarised as number and proportion. Continuous variables were summarised by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. For all efficacy endpoints, means and proportions with two-sided 95% confidence intervals (CI) were determined. On-treatment adherence was calculated by subtracting the number of missed doses from the total number of doses prescribed for therapy duration and dividing by the total number of doses prescribed for therapy duration. Sofosbuvir-velpatasvir adherence was calculated by pill count and self-reported questionnaire. In calculating adherence, pill count took precedence over self-report if discrepancies were noted. A participant was considered adherent if that individual received $\geq 95\%$ of scheduled doses for $\geq 95\%$ of the scheduled treatment period. Analysis was performed using SAS (Version 9.4, SAS Institute Inc, Carey, NC, USA) and STATA (version 15.0; StataCorp, College Station, TX).

Study oversight

All participants provided written informed consent before study procedures. The study protocol was approved by Royal Adelaide Hospital Human Research Ethics Committee (primary study committee), as well as through local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines. The study was registered with clinicaltrials.gov (NCT02625909).

Role of the Funding source

The study was funded by National Institutes of Health (NIH) (NIDA division). Study medication was provided by Gilead Sciences Inc. The sponsor (The Kirby Institute, UNSW Sydney) collected the data, managed study samples, monitored study conduct, performed the statistical analysis, and drafted the manuscript.

RESULTS

Baseline characteristics

Between March 2017 and July 2019, 277 individuals were assessed for eligibility. Of these 196 were enrolled and randomised, 97 individuals into the short arm and 99 individuals into the standard arm (Figure 1). Fifty-five individuals were excluded at screening, 38 (69%) of whom did not meet eligibility criteria, with most not meeting inclusion criteria for HCV RNA >10,000 IU/ml (**Supplementary Table 1**). Twenty-six individuals were enrolled, but not randomised at week six. In the majority (n=21/26, 80%), the reason for non-randomisation was the participant being before week six at time of DSMB recommendation to halt short arm. These participants were immediately extended to 12 weeks. Five individuals were not randomised due to lost to follow-up between baseline and week six. Of 196 people randomised, four individuals in the short arm were at the week six timepoint when the DSMB recommendation was made and were also immediately extended to 12 weeks therapy and excluded from the primary analysis. A further four participants correspondingly randomised to the standard arm at the time of the DSMB recommendation were also excluded from the primary analysis population. The final population for primary analysis thus consists of 188 participants, 93 in the short arm and 95 in the standard arm.

The demographic and clinical characteristics of participants were similar between the two arms (**Table 1**). Mean age was 44 years, and majority male (98%) and white (84%). Seventy-four percent identified as gay and 69% were HIV positive (100% on ART, median CD4 605 [IQR

474-798 cells/mm³). Sixty-three percent had primary HCV infection whilst just over a third (37%) presented with an HCV reinfection episode. The genotype distribution included 65% (n=122) genotype 1 (1a n=115; 1b n=6; 1, no subtype, n=1), 2% (n=4) genotype 2, 17% (n=32) genotype 3, and 16% (n=30) genotype 4. Median baseline HCV RNA was 5.6 log₁₀ IU/mL (IQR 4.6, 6.5), with baseline HCV RNA >1,000,000 IU/ml (>6 log₁₀) in 38% (n=72) and > 10,000,000 IU/ml (>7log₁₀) in 10% (n=18). Median duration of HCV infection at baseline was 26 weeks (IQR 17, 35).

The likely mode of HCV acquisition was deemed sexual exposure in 142 (76%), injecting drug use in 40 (21%), non-injecting drug use in 1 (0.5%), occupational exposure in 1 (0.5%), and other or unknown in 4 (2%). Of the sexual acquisitions, the majority (n=135/142, 95%) were same sex male-male exposures.

Risk behavioural characteristics

Most participants were in full-time employment (55%) and living in either privately owned (31%) or rental (58%) accommodation. Seventy-nine percent had undergone screening for sexually transmitted infection (STI) within the prior 12 months with 53% reporting a positive STI diagnosis (predominantly syphilis). A history of incarceration was reported in 29 participants (15%). Although IDU was reported as most likely mode of HCV acquisition in only 40 participants, 99 of 177 (56%) reported ever having injected drugs, and of these 48% injected in last 30 days, 28% in last 1-6 months, and 24% longer than 6 months ago. The most common drug used was methamphetamine (47%). Detailed description of risk behaviour characteristics is given in Supplementary Table 2.

Treatment efficacy

In the ITT population (n=188), the ETR was 85/93, 91.4% (95% CI 83.8-96.2) in the short arm and 87/95, 91.6% (95% CI 84.1-96.3) in the standard arm (an absolute difference in proportions

of 0.2, $p=0.905$). SVR12 in the short arm was 70/95, 81.7% (95% CI 72.4-89.0) and 80/95, 90.5% (95% CI 82.8-95.6) in the standard arm (Figure 2). The difference between the arms was -8.81 (95% CI: -18.6, 1.0) with the 95% lower confidence bound for the difference falling below the pre-specified level of 12%. Criteria for non-inferiority was therefore not met. Although non-inferiority was not shown, the difference in SVR12 rates between the arms in the ITT analysis was not significant ($p=0.080$). A variety of reasons for not achieving SVR12 were observed. Overall, two participants died (both in short arm), eight were lost to follow-up (three in short arm, five in standard arm), five were re-infected (three in short arm, two in standard arm) and 11 had virological relapse (nine in short arm, two in standard arm) (Suppl Table 3).

By modified ITT (mITT) analysis in which participants with non-virological failure were excluded (including death, reinfection, lost to follow-up), SVR12 was 76/85, 89.4% (95%CI 80.8-95.0) in the short arm and 86/88 97.7% in the standard arm (95%CI 92.3-99.7; difference -8.3, $p=0.025$).

In a further per-protocol analysis which included only participants who were >90% adherent and attended an SVR12 visit (excluding participants who were reinfected or retreated), SVR12 was 93.2% (95%CI 84.9-97.8) in the short arm and 100% (95%CI 95.5-100.0) in the standard arm ($p=0.020$).

Sixteen participants did not achieve ETR by ITT analysis of which eight participants were in each arm. In the standard arm all of eight participants were considered ETR failures due to missing data (4 of these achieved subsequent SVR12, 3 remained missing data and one patient had virological failure at SVR12). In the short arm two were due to missing data and six had detectable virus measured at ETR. All but one of these six patients with detectable virus

subsequently achieved SVR12. Thus only one patient with documented detectable virus at ETR subsequently had virological failure.

Virological recurrence

Sixteen participants within the study experienced virological recurrence at or before SVR12, 12 in the short arm and four in the standard arm. Sequencing from baseline and time of recurrence was performed in all 16. Five participants were identified as having reinfection – four on the basis of a genotype switch (1a to 3a, 1a to 4d, 3a to 1a, 4d to 1a) and one with the same genotype (1a) at both timepoints but with a genetic distance that indicated heterologous virus at relapse (11.4% in core-E2, 9.4% in NS5A). Eleven (5.8%) participants were classified as relapse (9 [9.6%] in short arm, two [2.0%] in standard arm). All had homologous virus at time of relapse with a genetic distance in core-E2 of $< 1.5\%$ compared to baseline. Characteristics of the participants with reinfection and relapse are given in Table 2. Although limited by small numbers, no clear association with baseline characteristics was observed, although those with relapse did have a higher median baseline HCV RNA ($6.7 \log_{10}$ IU/mL, $6.8 \log_{10}$ IU/mL for just those in 6 weeks arm) and longer estimated duration of infection (30 weeks across both arms) than those who did not ($5.5 \log_{10}$ IU/mL and 25 weeks, respectively). The proportion with baseline HCV RNA $> 7 \log_{10}$ IU/mL was 8% in the study population overall but 36% in the small group who relapsed. All but one of the participants with relapse was $>95\%$ adherent to therapy. One participant in the standard arm took only four weeks of treatment and subsequently relapsed. Of the eleven participants with virological failure, eight were detected as virological relapse by SVR4, one at SVR12 having been not detected at SVR4, and two did not attend for an SVR4 visit.

Adherence

Overall adherence within the study was good, although was higher in the short versus standard arm. Adherence at a level of >80% and >95% was observed in 97% and 95% of participants in the short arm, and 91% and 84% of those in the standard arm ($p=0.13$ and 0.031 for >80% and >95% comparisons, respectively)(Table 3).

Resistance and retreatment

All 11 participants with virological relapse were sequenced for the development of NS3 and NS5A resistance associated substitutions (RAS). Six participants had no evidence of resistance with wild type virus at baseline and relapse. Three participants had RAS at baseline that remained unchanged at relapse (M31L, $n=1$ (GT4d); Q30H + Y93H (Gt1a), $n=1$; 62T, $n=1$ (Gt3a)). One participant had Y93H at baseline (GT4d) that had reverted to wild type at relapse and one participant had no RAS at baseline and L31M at relapse (GT1a, short arm). Thus, only one of 11 participants with virological relapse potentially had treatment emergent resistance following short-course treatment (L31M). Of the 11 participants with virological relapse, nine were retreated. Retreatment regimens included sofosbuvir-velpatasvir-voxilaprevir (12 weeks, $n=4$), sofosbuvir-velpatasvir (12 weeks, $n=1$) and glecaprevir-pibrentasvir (8 weeks, $n=4$). All achieved SVR12 apart from one whose outcome was unknown due to loss to follow-up.

Safety

In the randomised population of 188 participants, two deaths occurred, both in the short arm and occurred following the SVR4 timepoint (at which both participants had undetectable HCV RNA). The cause of death was illicit drug use plus ischaemic heart disease in one and unknown in the other; neither were considered treatment related given they occurred at least 1 month following treatment cessation. Overall, 55% of participants experienced at least one adverse event (AE), but only 23% experienced a treatment-related AE (22 in short arm; 21 in standard arm). Ninety-eight per cent of treatment-related AEs were Grade 1-2 with only one Grade 3 treatment related AE and no Grade 4 events. The only AE occurring in > 10% of the study population was fatigue, reported in 11.2% of people. Serious adverse events (SAEs) were reported in 6 participants – one in the short arm and five in the standard arm (Supplementary

Table 4), only one was considered a possible treatment related SAE. This participant experienced an episode of rhabdomyolysis (rash and raised creatinine kinase) one week after commencing medication and was briefly hospitalised. Although the SAE was considered possibly treatment-related and the participant was advised to stop taking treatment, medication was continued, and the episode spontaneously resolved with full completion of therapy. Therefore, no participant discontinued treatment due to adverse events. Six participants discontinued treatment for non-safety reasons, five were lost to follow-up during the treatment period (all in the second half of therapy in the standard arm), two of whom subsequently returned for subsequent visits; one decided not to continue treatment and was subsequently lost to follow-up by SVR12 (also in standard arm).

DISCUSSION

In this randomised study of shortened treatment duration for individuals with recent HCV, sofosbuvir-velpatasvir for six weeks failed to meet the pre-specified criteria for non-inferiority and the study was terminated early following the second DSMB review. The sub-optimal efficacy in the short arm was driven largely by a higher post-treatment relapse, observed in 10% (n=9) of participants compared with 2% (n=2) of participants in the standard arm. The REACT study thus found a six-week course of the pan-genotypic regimen sofosbuvir-velpatasvir did not reach non-inferiority against the standard 12-week duration in the setting of recently acquired HCV infection and cannot be considered as effective as the 12-week course.

Although virological relapse was higher in the short compared to the standard arm, there were only 11 participants in total with this endpoint, thus limiting power to detect associations. Those with relapse were slightly older, had higher baseline HCV RNA and marginally longer duration of HCV. Although none of these factors could be definitively associated with failure it is of note that the median baseline HCV RNA was 1.3log higher in the 6 week relapsers than in patients

who achieved SVR12, and the median duration of infection was 5 weeks longer. This may suggest that patients without these negative prognostic factors may indeed do well with shortened therapy. Failure did not appear linked to the presence of RAS at baseline. Seven of the 11 participants with relapse had wild type at baseline and only one gained a RAS (L31M) at the failure timepoint. This participant was successfully retreated with sofosbuvir-velpatasvir-voxilaprevir for 12 weeks. Retreatment was left to the discretion of the site investigator and it is noteworthy that almost all participants were retreated and achieved SVR12. These findings are encouraging for salvage from short course therapy and confirm previous findings from studies in chronic HCV infection.(21)

Short course therapy (4-6 weeks) for both acute and chronic HCV infection has been explored using a number of DAA regimens with varying success.(9, 12, 14, 22, 23) In established chronic HCV infection results have generally been sub-optimal, one exploratory study reporting SVR rates in the region of 20-40% with three and four DAA agent regimens(23). In a small study (n=16) of young PWID with early liver disease (age <50 years, LSM < 8.0kPa) in Denmark using four weeks of sofosbuvir-ledipasvir plus ribavirin, SVR12 was higher at 93% by per protocol analysis with just one case of relapse (SVR12 ITT 75%).(24) A subsequent study by the same group and in the same target population demonstrated similar results using a combination of glecaprevir-pibrentasvir plus ribavirin with an ITT SVR of 75%.(25) A lower ITT SVR of 59% was observed in 17 patients treated with four weeks glecaprevir-pibrentasvir alone. Results with short course DAA therapy in the setting of acute and recent HCV infection have been more encouraging, although again somewhat varied. Two studies from Germany, one in HIV negative and one in HIV positive participants, evaluated sofosbuvir-ledipasvir for six weeks for acute HCV infection with genotype 1 or 4 demonstrating an ITT SVR of 100% and 77%, respectively.(10, 11) A further larger study in genotype 1 and 4 using 8 weeks of grazoprevir-elbasvir, the DAHHS2 study, confirmed extremely high SVR with only one virological failure in

80 HIV positive participants.(15) TARGETSD, the only study to date using a pan-genotypic regimen, contained only one virological failure in a smaller group of 30 individuals treated with six weeks glecaprevir-pibrentasvir.(14) None of these studies was randomised and a variety of different definitions were used to characterise the often-heterogeneous study populations. In contrast, REACT is a randomised study evaluating the pan-genotypic regimen of sofosbuvir-velpatasvir; although the results appear conclusive, the study was not powered to look at differences within sub-populations and results cannot be extrapolated to all regimens and settings.

In the context of treatment of recent HCV infection among high-risk populations, there is clearly subsequent risk for HCV reinfection. Reinfections were observed in five (2.6%) participants at or prior to SVR12, with four identified by genotype switch and one with same genotype confirmed through sequencing and genetic diversity evaluation. The study population had high levels of sexual and injecting risk. Although IDU was identified as the most likely route of HCV in only 21%, a history of injecting drugs was reported by 56%, 75% of whom had injected in the prior six months. Methamphetamine was overwhelmingly the commonest drug injected. In relation to sexual risk, over half (53%) of participants reported an STI in the prior 12 months and just under half (48%) of the HIV negative population were receiving pre-exposure prophylaxis (PrEP). New HCV acquisitions among gay and bisexual men using PrEP appear to be increasing in several European countries,(26-28) and HCV testing should be considered as part of a routine sexual health check among those taking PrEP. Post-SVR12, HCV RNA testing was performed three-monthly for up to 24 months in the REACT population and will provide important further insights regarding populations at risk for reinfection.

Within the REACT cohort, no safety issues were identified and adherence to therapy and protocol were high. Adverse events reported were mild and no participant had to discontinue

therapy due to side effects. Adherence was high and not a factor in most treatment failures.

Ninety-three per cent of participants took more than 80% of doses and 90% took more than 95% of doses. Interestingly, adherence was higher in the short arm, suggesting that short duration therapy may have advantages in terms of treatment completion. Lost to follow-up rates were also low – only eight (4%) participants were lost before SVR12. This may in part reflect that in some REACT sites, treatment for recent HCV could only be accessed through clinical trial protocols providing additional motivation for protocol adherence, and in many sites participants were already enrolled in regular HIV care and/or opioid substitution programs. It is also true that some participants (n=5) were lost on-treatment prior to randomisation and are not included in this analysis.

Although this was a relatively large randomised trial, it does have a number of limitations impacting on our ability to make broad generalisations. Firstly despite attempts to include sites likely to see a variety of individuals with HCV acquisition, including the addition of extra sites during the study period, the study population was overwhelmingly male, limiting its generalisability to females. Similarly, most participants were HIV positive and not infected through IDU. This group may be different in engagement to HIV negative people who inject drugs, particularly in terms of patterns of drug use. Relatively few (17%) were injecting opioids although this is now the greatest source of new HCV infections across the United States. (29) Future studies should address this expanding epidemic and the role of short course therapy in this population. Third, the study population included a heterogeneous group of patients with recently acquired infection, including acute patients and those with symptomatic and asymptomatic infection. Although the small number of overall failures limited the ability to draw conclusions within sub-populations there was only one relapse patient in each arm with duration of infection less than six months at treatment commencement while most participants had a duration of

infection > 6 months (median 20 weeks). Finally, sofosbuvir-velpatasvir is the only regimen evaluated in this study.

Engagement of individuals early in HCV infection is crucial for HCV elimination efforts. Despite higher relapse in the short arm, REACT confirms that treatment initiated early in infection is safe, feasible and highly effective. Even with a relapse rate of 10% in the short arm, generation of resistance was limited and almost all participants were able to be quickly and successfully retreated. Nevertheless, acknowledging the caveats on generalizability above, REACT clearly demonstrates that at least in this predominantly HIV positive population 6 weeks of sofosbuvir/velpatasvir is suboptimal and patients should be treated with at least 8 weeks duration (30). REACT provides important data on HCV therapeutic intervention outcomes for recent infection among a high-risk population, with implications for individual care and HCV elimination strategies.

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Figure 1: Participant disposition**Figure 2: Virological outcomes at end of treatment and SVR12****Figure 2A. End of treatment response (ETR) and SVR12 outcomes by intent-to-treat (ITT) analysis**

Proportion of patients achieving ETR and SVR12 are given in solid bars with 95% CI for each outcome represented by line bars. Difference in proportions between the two arms (represented by horizontal line with 95% CI) at ETR $p=0.965$ and SVR12 ITT $p=0.080$ (test for equality of proportions)

Figure 2B. SVR12 outcomes by modified ITT (mITT) and per-protocol (PP) analyses

Proportion of patients achieving SVR12 by modified ITT (mITT) and per protocol (PP) analyses are given in solid bars with 95% CI for each outcome represented by line bars. Difference in proportions between the two arms (represented by horizontal line with 95% CI) at SVR12 (mITT) $p=0.025$ and SVR12 (PP) $p=0.020$ (test for equality of proportions)

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Table 1: Participant demographic and clinical enrolment characteristics

	Short duration 6 weeks		Standard duration 12 weeks		Total	
	N=93	%	N=95	%	188	%
Gender						
Female	2	2.2	4	4.2	6	3.2
Male	91	97.8	91	95.8	182	96.8
Recent HCV infection						
Primary infection	59	63.4	60	63.2	119	63.3
Reinfection	34	36.6	35	36.8	69	36.7
Race						
Caucasian/White	79	84.9	78	82.1	157	83.5
Asian	4	4.3	4	4.2	8	4.3
Black or African American	0	0.0	2	2.1	2	1.1
Other	9	9.7	8	8.4	17	9.0
Unknown or not reported	1	1.1	3	3.2	4	2.1
Ethnicity						
Hispanic or Latino	3	3.2	8	8.4	11	5.9
Not Hispanic or Latino	89	95.7	87	91.6	176	93.6
Unknown or not reported	1	1.1	0	0.0	1	0.5
HIV positive	65	69.9	65	68.4	130	69.1
Age (mean, SD)	44.2	10.3	43.4	10.2	43.8	10.2
Baseline HCV RNA, log₁₀ IU/mL (median, IQR)	5.6	4.8-6.5	5.4	4.3-6.3	5.6	4.6-6.5
HCV genotype						
1a	58	62.4	57	60.0	115	61.2
1b	4	4.3	2	2.1	6	3.2
1 unknown subtype	1	1.1	0	0	1	0.5
2	0	0.0	4	4	4	2.1
3	15	16.1	17	17.9	32	17.0
4	15	16.1	15	15.8	30	15.9
Mode of HCV exposure#						
Injecting drug use	18	19.4	22	22.2	40	21.3
Sexual exposure with person(s) of opposite sex	3	3.2	4	4.2	7	3.7
Sexual exposure with person(s) of same sex	69	74.2	66	69.5	135	71.8
Occupational (needle stick or other exposure)	0	0.0	1	1.1	1	0.5
Use of non-injectable recreational drugs	1	1.1	0	0.0	1	0.5
Other, specify*	2	2.2	2	2.1	4	2.1
Max ALT (median, IQR)	364	152-799	360	155-871	362	154-847
Baseline ALT (median, IQR)	114	56-257	128	69-222	126	62-250
Symptomatic presentation	16	17	14	15	30	16
Estimated duration of infection to baseline (weeks, median, IQR)	26.1	17-33.8	25.0	17-35.4	25.8	17-35.2
Injecting drug use characteristics:						

Total respondents	66		67		177	
Injecting drug use, n (%)						
Never	38	43.2	40	44.9	78	44.1
Ever (total of the groups below)	50	56.8	49	55.1	99	55.9
Not recent (Last injected >6 months ago) ¹	10	20	14	28.5	24	24.2
Recent (Last injected between 1-6 months ago) ¹	14	28	14	28.	28	28.3
Current (Last injected within 30 days) ¹	26	52	21	42.9	47	47.5
In those reporting injecting drug use:	Medi	IQR	Medi	IQR	Medi	IQR
Age at first injecting, median (range)	34.5	(24-43)	32	(19-40)	33	(21-42)
If injected in the previous 1 month, frequency (n, %)²:	N	%	N	%	N	%
>3x most days	0	0	0	0	0	0
2-3x most days	3	11.5	2	9.5	5	10.6
Daily	2	7.7	1	4.8	3	6.4
More than weekly, but less than daily	4	15.4	4	19.0	8	17.0
Less than weekly	9	34.6	9	42.9	18	38.3
Missing	2	7.7	2	9.5	4	8.5
Drug injected most in last month, n (%)²						
Heroin	0	0.0	5	23.8	5	10.6
Cocaine	1	3.8	0	0.0	1	2.1
Methamphetamines (ice, base, speed, meth crystal)	12	46.2	10	47.6	22	46.8
Morphine	1	3.8	1	4.8	2	4.3
Other	3	11.5	0	0.0	3	6.4
Fentanyl	1	3.8	0	0.0	1	2.1
Missing	8	30.8	5	23.8	13	27.7
Opioid substitution therapy, n (%)³						
Never	73	83.0	76	85.4	149	84.2
Ever:	12	13.6	8	9.0	20	11.3
<i>Current</i>	3	3.4	5	5.6	8	4.5
<i>Not current</i>	9	10.2	3	3.4	12	6.8

* Jail, unknown, accidental needle stick, nasal drug use (also reported sexual exposure with other known to be HCV positive and use of non-injectable rec drugs)

Mode of exposure determined by clinician

Denominators: 1 – ever injected; 2 – current (injected in last 30 days); 3 – all survey respondents

Table 2: Characteristics of participants with virological failure at SVR12

Subject	Reason for Viral recurrence at SVR 12	Gender	Recent infection status at BL	Initial GT	GT at recurrence	Baseline HCV RNA (log IU/ml)	HCV Mode of exposure	HIV positive	Adherent (>95%)	Estimated duration of infection to BL - days	Age (years)
Standard Arm											
1	RELAPSE	Male	Reinfection	1b	1b	5.96	IDU	No	No	221	57
2	REINFECTION	Male	Reinfection	1a	3a	5.00	IDU	No	Yes	380	27
3	REINFECTION	Male	Reinfection	1a	4d	6.77	Sexual	Yes	Yes	154	52
4	RELAPSE	Male	Primary	4d	4d	6.92	Sexual	Yes	Yes	134	55
Shortened Arm											
1	RELAPSE	Male	Primary	1a	1a	7.43	Sexual	Yes	Yes	178	57
2	RELAPSE	Male	Reinfection	3a	3a	5.58	IDU	No	Yes	228	56
3	RELAPSE	Male	Primary	1a	1a	6.14	Sexual	Yes	Yes	208	32
4	RELAPSE	Male	Reinfection	1a	1a	6.53	Sexual	Yes	Yes	245	46
5	RELAPSE	Male	Reinfection	1a	1a	6.81	Sexual	Yes	Yes	249	47
6	REINFECTION	Male	Reinfection	1a	1a	5.74	Sexual	Yes	Yes	237	51
7	RELAPSE	Male	Primary	1a	1a	7.10	Sexual	Yes	Yes	228	45
8	RELAPSE	Male	Primary	1a	1a	7.22	Sexual	Yes	Yes	175	57
9	RELAPSE	Male	Primary	4d	4d	7.20	Sexual	Yes	Yes	85	43
10	REINFECTION	Male	Reinfection	3a	1a	3.78	Sexual	Yes	Yes	140	45
11	REINFECTION	Male	Primary	4d	1a	5.40	Sexual	Yes	Yes	229	46
12	RELAPSE	Male	Reinfection	1a	1a	6.69	IDU	Yes	Y	183	53

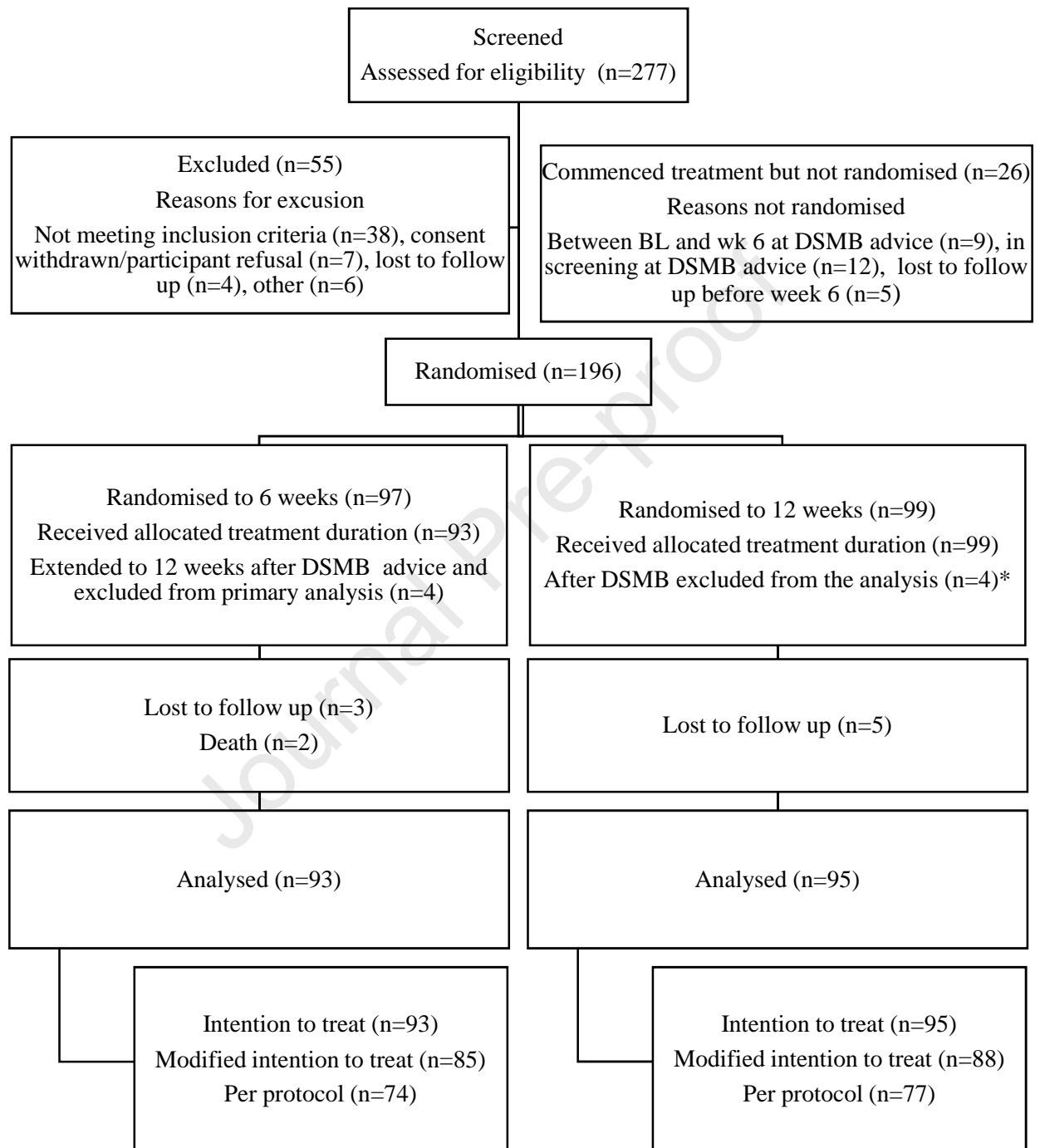
BL: Baseline; IDU: Injecting drug use; GT: Genotype

Table 3. On treatment adherence

	N adherent	%	L95%CI	L95%CI	p-value diff (Arm 1 vs 2)
80% adherence					0.136
Short Arm	90	96.77	90.86	99.33	
Standard Arm	86	90.52	82.78	95.58	
90% adherence					0.250
Short Arm	89	95.70	89.35	98.82	
Standard Arm	86	90.52	82.78	95.58	
95% adherence					0.031
Short Arm	88	94.62	87.90	98.23	
Standard Arm	80	84.21	75.30	90.81	
100% adherence					0.025
Short Arm	78	83.87	74.80	90.68	
Standard Arm	66	69.47	59.18	78.53	

Difference in proportion – Fisher’s exact p value

Figure 1.



* These 4 participants were randomised to 12 weeks within the same timeframe as the 4 participants in short arm who were at randomisation and extended following DSMB advice and therefore excluded from the analyses.

Figure 2A

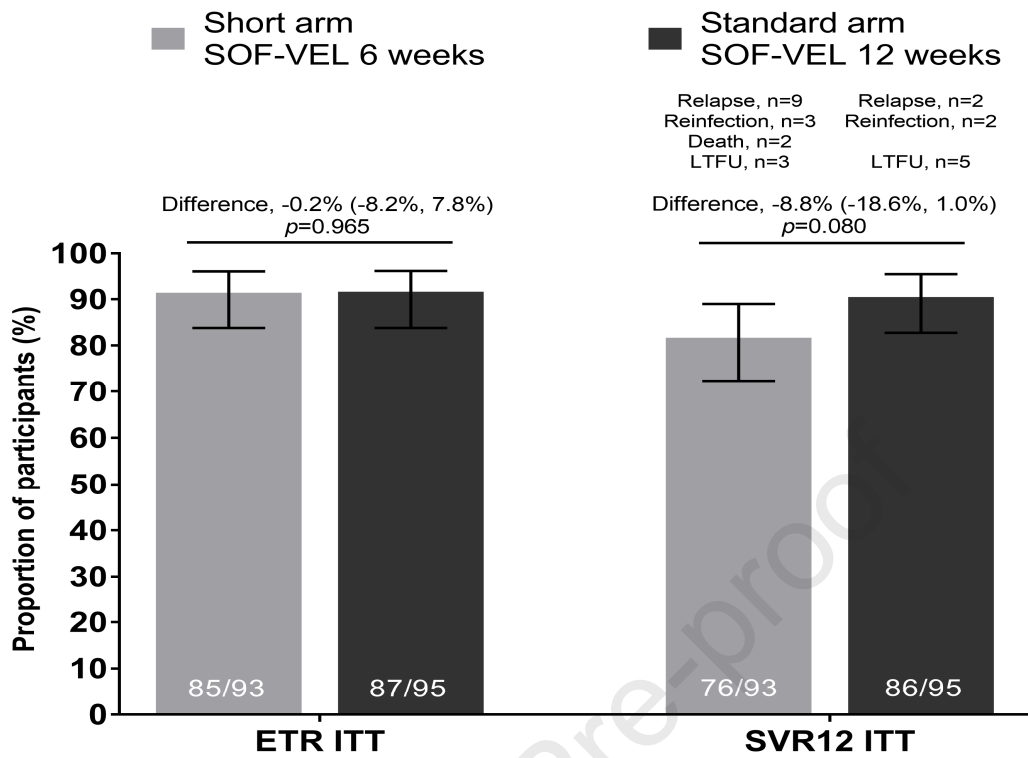
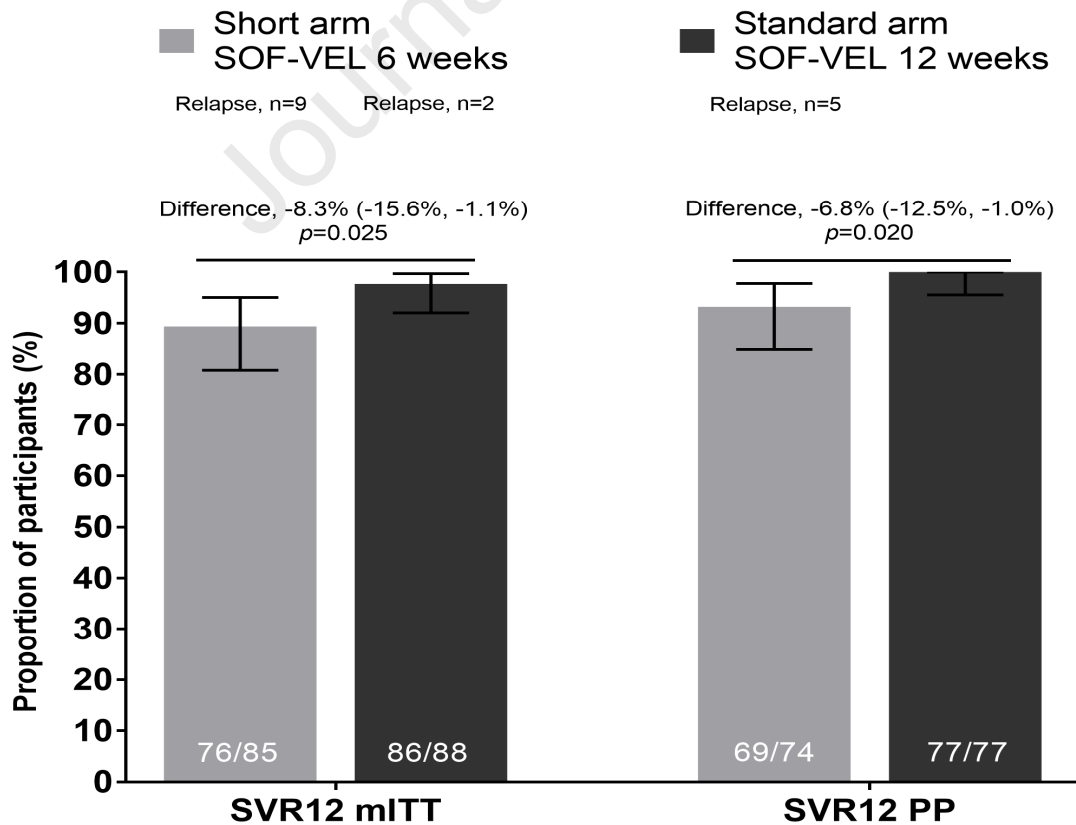


Figure 2B



Highlights

- REACT is a randomised study of short course DAA therapy for recently acquired HCV
- 188 participants were treated with either 6 or 12 weeks sofosbuvir/velapatasvir
- Study population was predominantly cis-male with a high proportion living with HIV
- The study was stopped early due to high rate of virological relapse in the short arm.
- Six weeks of sofosbuvir/velapatasvir cannot be considered non-inferior to 12 weeks.

Journal Pre-proof