Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial

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Abstract: BACKGROUND AIMS Direct-acting antiviral (DAA) therapy for HCV has high efficacy and limited toxicity. We hypothesised that the efficacy of glecaprevir-pibrentasvir for chronic HCV with a simplified treatment monitoring schedule would be non-inferior to a standard treatment monitoring schedule. METHODS In this open-label multicentre phase IIIb trial, treatment-naïve adults with chronic HCV without cirrhosis were randomly assigned (2:1) to receive glecaprevir-pibrentasvir 300 mg-120 mg daily for 8 weeks administered with a simplified or standard monitoring strategy. Clinic visits occurred at baseline and post-treatment week 12 in the simplified arm, and at baseline, week 4, week 8, and post-treatment week 12 in the standard arm. Study nurse phone contact occurred at week 4 and week 8 in both arms. Participants requiring adherence support were not eligible, including those reporting recent injecting drug use. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12), with a non-inferiority margin of 6%. RESULTS Overall, 380 participants (60% male, 47% genotype 1, 32% genotype 3) with chronic HCV were randomised and treated with glecaprevir-pibrentasvir in the simplified (n = 253) and standard (n = 127) arms. In the intention-to-treat population, SVR12 was 92% (95% CI 89%-95%) in the simplified and 95% (95% CI 92%-99%) in the standard arm (difference between arms -3.2%; 95% CI -8.2% to 1.8%) and did not reach non-inferiority. In the per-protocol population, SVR12 was 97% (95% CI 96%-99%) in the simplified and 98% (95% CI 96%-100%) in the standard arm. No treatment-related serious adverse events were reported. CONCLUSIONS In patients with chronic HCV infection without cirrhosis, treatment with glecaprevir-pibrentasvir was safe and effective. In comparison to standard monitoring, a simplified monitoring schedule did not achieve non-inferiority. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT03117569. LAY SUMMARY Direct-acting antiviral (DAA) therapy for hepatitis C is highly effective and well tolerated. The SMART-C randomised trial evaluated an 8-week regimen of glecaprevir-pibrentasvir for hepatitis C treatment, using a simplified monitoring schedule that included no pathology tests or clinic visits during treatment. This simplified strategy produced a high cure rate (92%), but this was not equivalent to the standard monitoring schedule cure rate (95%).

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Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial

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Abstract

Background and aims: Direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) has high efficacy and limited toxicity. We hypothesised that efficacy of glecaprevir-pibrentasvir for chronic HCV with a simplified treatment monitoring schedule would be non-inferior to a standard treatment monitoring schedule.

Methods: In this open-label multicentre phase 3b trial, treatment-naïve adults with chronic HCV without cirrhosis were randomly assigned (2:1) to receive glecaprevir-pibrentasvir 300mg-120mg daily for eight weeks administered with a simplified or standard monitoring strategy. Clinic visits occurred at baseline and post-treatment week 12 in the simplified arm, and at baseline, week four, week eight, and post-treatment week 12 in the standard arm. Study nurse phone contact occurred at week four and week eight in both arms. Participants requiring adherence support were not eligible, including those reporting recent injecting drug use. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12), with a non-inferiority margin of 6%.

Results: Overall, 380 participants (60% male, 47% genotype 1, 32% genotype 3) with chronic HCV were randomized and treated with glecaprevir-pibrentasvir in the simplified (n=253) and standard (n=127) arms. In the intention-to-treat population, SVR12 was 92% (95% CI 89%, 95%) in the simplified and 95% (95%CI 92%, 99%) in the standard arm (difference between arms, -3.2%; 95%CI -8.2%, 1.8%), and did not reach non-inferiority. In the per-protocol population, SVR12 was 97% (95%CI 96%, 99%) in the simplified and 98% (95%CI, 96%, 100%) in the standard arm. No treatment-related serious adverse events were reported.

Conclusions: In patients with chronic HCV infection without cirrhosis, treatment with glecaprevir-pibrentasvir was safe and effective. In comparison to standard monitoring, a simplified monitoring schedule did not achieve non-inferiority.

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INTRODUCTION

Globally, an estimated 71 million people have chronic hepatitis C virus (HCV) infection.[1] HCV treatment was interferon-based for more than two decades, with the addition of ribavirin,[2] pegylated-interferon,[3] and first-generation protease inhibitor direct acting antiviral (DAA) therapies (telaprevir, boceprevir),[4,5] providing stepwise improvements in efficacy as defined by sustained virological response (SVR). Despite these improvements, treatment uptake remained low in most countries, with <1% to 5% of people with chronic HCV initiating therapy each year.[6]

Recent years have seen a revolution in HCV therapeutic development, with the availability of interferon-free DAA regimens.[7] Simple (once daily dosing oral regimens), well tolerated, short-duration (8-12 weeks), pangenotypic DAA therapy with high efficacy (cure rates above 95%) is now standard of care for chronic HCV. The broad implementation of DAA therapy has considerable public health potential, with the World Health Organization setting ambitious HCV elimination impact targets for reductions in HCV incidence (80%) and liver disease mortality (65%) by 2030.[8]

The capacity to scale-up DAA therapy should be enhanced by simplified treatment monitoring strategies. The coformulation of glecaprevir-pibrentasvir, an NS3/4a protease inhibitor and NS5A inhibitor combination, provides key features for HCV treatment simplification, including on-treatment monitoring: 1) pan-genotypic activity with high efficacy; 2) minimal drug-related toxicity; 3) ease of dosing (three pills once daily); and 4) short duration (eight weeks for patients without cirrhosis). In phase 3 clinical trials among people without cirrhosis, an eight week regimen of glecaprevir-pibrentasvir (300mg-120mg) provided SVR rates of 95-100% in HCV genotypes 1-6.[9,10]

We hypothesised that in treatment naïve patients with chronic HCV (genotypes 1-6) the sustained virological response rate 12 weeks following treatment with glecaprevir-pibrentasvir among those receiving a simplified monitoring schedule would be non-inferior to that in those receiving a simplified monitoring schedule on the intention-to-treat population.

METHODS

Study design and randomisation

In this open-label international multicentre phase 3b trial, treatment-naïve adults with chronic HCV and without cirrhosis were randomly assigned (2:1) to receive glecaprevir-pibrentasvir 300mg-120mg for eight weeks administered with a simplified or standard monitoring strategy (SMART-C; Figure 1). Randomisation was computer-generated and stratified according to HCV genotype (genotype 1 or non-genotype 1) and country. The treatment assignments were not concealed. Glecaprevir-pibrentasvir was administered orally once daily as three fixed-dose combination tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, for a total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir.

Participants

From 21 August 2017 to 16 July 2018, participants were screened and enrolled at 33 sites in Australia (n=6), Canada (n=7), France (n=3), Germany (n=4), New Zealand (n=4), Switzerland (n=2), United Kingdom (n=3), and United States (n=4). Study recruitment was conducted through a network of tertiary specialist viral hepatitis clinics (n=30), and primary care clinics (n=3). Scheduled study follow-up continued through 14 December 2018, when the final participant enrolled underwent sustained virological response assessment 12 weeks following treatment.

Participants who were at least 18 years of age were eligible for participation if they had chronic HCV genotypes 1-6, were HCV treatment-naïve (interferon-based or DAA), and did not have cirrhosis. The absence of cirrhosis in all participants was assessed by means of transient elastography or AST-to-platelet ratio index (APRI). Absence of cirrhosis was defined as liver stiffness measurement by transient hepatic elastography of <12.5 kPa or APRI of <1.0.

Individuals receiving opiate agonist therapy and those with HIV co-infection were eligible. Participants who were considered by their clinician to require additional treatment adherence support were not eligible, although a standardised adherence assessment tool was not used across sites. The suitability for enrolment in relation to perceived adherence support needs was based on clinical judgement and was at the discretion of site investigator, reflecting clinical practice and enhancing generalisability. Participants who self-reported injecting drug use within the previous six months or those who tested positive on urinary drug screen (UDS) at screening were not eligible. Individuals with acute or chronic hepatitis B co-infection (hepatitis B surface antigen positive) were excluded. Participants with prior hepatitis B infection (hepatitis B surface antigen negative, anti-hepatitis B core antibody positive) were eligible. Full eligibility criteria are provided in the study protocol, available with the full text of this article in the *Supplementary Material*.

Study assessments

In the standard arm, scheduled clinic study visits were undertaken at baseline, treatment weeks four and eight (end of treatment), and post-treatment week 12. In the simplified arm, scheduled clinic study visits were undertaken at baseline and post-treatment week 12. Assessments at these visits included measurement of vital signs, symptom-directed physical examinations, assessment of HCV RNA, and standard laboratory testing. In the standard arm, study drug was dispensed at baseline and treatment week four. In the simplified arm, study drug was fully dispensed at baseline. To standardise reporting and data collection, in both the standard and simplified arms, phone contact was initiated by the study nurse at weeks four and eight (end of treatment) to monitor treatment adherence and adverse events using a structured case report form and questionnaire. For participants in the standard arm, phone contact was initiated one to two days prior to their planned clinic visit at weeks four and eight. All adverse events were

recorded and graded according to a standard scale (see study protocol for details). Study drug adherence was assessed by self-reported adherence questionnaires at weeks four and eight (phone contact), and pill count at week eight (standard arm) or post-treatment week 12 (simplified arm). Participants were asked to return study drug packaging (and any unused medication) at end of treatment (standard arm) or post-treatment week 12 (simplified arm), with the number of pills returned recorded by the site coordinator and pharmacist.

The presence of HCV RNA in plasma was assessed at all scheduled clinic study visits using Aptima HCV Quant Dx assay, version 2.15.5 (lower limit of quantitation [LLoQ] 10IU/mL; Hologic, Inc., Marlborough, MA, USA), with centralised testing performed at St Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia). Reverse transcription of RNA with random hexamers was performed using the Invitrogen Superscript™ system (Vilo IV), and the Core-E2, NS5A and NS3 HCV regions were amplified by polymerase chain reaction.[11,12] Sanger sequencing was performed at the Australian Genome Research Facility on the Applied Biosystems™ 3730xl DNA Analyzer. Sequence curation was performed using RECall.[13] The presence of polymorphisms in NS3 and NS5A at baseline was evaluated using Geno2PhenoHCV. Among participants with virological failure, substitutions (relative to an individual's baseline HCV sequence) that developed on treatment were examined.

Study definitions

Stage of liver fibrosis was assessed by liver stiffness measurement (transient elastography [FibroScan®]) or APRI. For liver stiffness measurements, the chosen cut-offs for significant liver fibrosis and cirrhosis were 7.1 kPa and 12.5 kPa, respectively.[14] APRI below 1.0 excluded cirrhosis with high specificity.[15]

HCV virological suppression was defined as HCV RNA below the 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).

HCV treatment outcome was classified as SVR12 (defined as HCV RNA below the LLoQ at or after 12 weeks post cessation of treatment), 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). In the standard monitoring arm, HCV virologic failure was further defined as on-treatment failure (non-response or breakthrough) or post-treatment relapse (presence of quantifiable HCV RNA after end of treatment with detection of infection with an HCV strain consistent with the primary infecting strain, confirmed as homologous virus on sequencing). 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.

Study endpoints

The primary endpoint was SVR12 by intention-to-treat following glecaprevir-pibrentasvir for eight weeks administered with a standard compared to simplified monitoring schedule among people with chronic HCV who were treatment naïve and did not have cirrhosis. Secondary endpoints included premature treatment discontinuation, treatment adherence, and treatment-emergent serious adverse events.

Statistical analysis and sample size

A total of 375 participants (2:1 randomisation) were planned for enrolment and evaluation as the intention-to-treat population. With these participant numbers and under the assumption that the proportion achieving SVR12 would be 96% in both arms, the study had approximately 80% power to show non-inferiority of the simplified monitoring strategy as compared to the standard monitoring strategy, with a lower confidence bound for SVR12 in the simplified monitoring arm greater than 90% or with a lower confidence bound for the difference (simplified arm minus standard arm) in SVR12 greater than -6%. The 90% threshold for non-inferiority in the standard monitoring arm was based on the clinical trial data available at the time of study design (SVR12 96%), minus a 6% non-inferiority margin.[9,16] The non-inferiority margin of 6% was selected in accordance with the principles outlined in guidance on conducting non-inferiority trials;[17,18] the choice of margin ensured minimal to no loss of efficacy.

Primary efficacy and safety data were analysed in the intention-to-treat (ITT) population (all enrolled participants for efficacy and safety, as all received study drug), with loss to follow-up deemed treatment failure. The modified intention-to-treat (mITT) population included participants in the ITT population, but excluded those who did not attend follow up at or after post-treatment week 12. The per-protocol (PP) population included participants who completed the prescribed eight-week treatment course and attended follow-up post treatment. SVR12 assessment was nominally set at day 84 post treatment, with a lower limit of day 70 post-treatment. The upper limit was not specified and was set to study close.

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. Adherence was measured by self-reported adherence questionnaire (on-treatment week four and eight) at phone contact visits, and by pill count at post-treatment week 12. 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. By pill count and self-reported questionnaire, glecaprevir-pibrentasvir adherence was individually calculated at the 90/90 and 95/95 levels, defined as receipt of ≥90% or ≥95% of scheduled doses for ≥90% or ≥95% of the scheduled treatment period, respectively. In calculating adherence, pill count took precedence over self-report if discrepancies were noted. A participant was considered adherent if that individual received ≥95% of scheduled doses for ≥95% of the scheduled treatment period. Analysis was performed using 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 St. Vincent's Hospital, Sydney 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 (NCT03117569).

Role of the Funding source

The study (including study medications) was funded by a research grant from AbbVie. 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

Of 433 participants screened between 21 August 2017 to 16 July 2018, 380 were enrolled and randomised into the simplified (n=253) and standard (n=127) arms (Figure 2). Of the 53 participants excluded at screening, 43 (81%) did not meet eligibility criteria, most commonly due to HCV RNA < 10,000 IU/mL (n=18), and positive urinary drug screen (n=10) (Supplementary Table 2).

The demographic and clinical characteristics of enrolled participants were similar between the arms (Table 1). Overall, median age was 51 years, and 39% were female. The genotype distribution included 47% (n=179) genotype 1 (1a 33%, n=124; 1b 13%, n=51; 1, no subtype, n=4), 14% (n=52) genotype 2, 32% (n=121) genotype 3, 5% (n=18) genotype 4, <1% (n=1) genotype 5, and 2% (n=8) genotype 6. One participant had an indeterminate genotype. Median baseline HCV RNA was 6.3 $\log_{10}$ IU/mL (IQR 5.4, 7.0), with baseline HCV RNA >1,000,000 IU/ml (>6 $\log_{10}$) in 59% (n=101) and >10,000,000 IU/mL (>7 $\log_{10}$) in 22% (n=83). HIV co-infection was documented in 7% (n=27), with median CD4 count 698 cells x 10^6/L and HIV viral load below 50 copies/mL in 89% (n=24; three participants had missing results at screening). All participants with HIV were receiving antiretroviral therapy (n=27) (Supplementary Table 5).

Among all participants enrolled, the prevalence of polymorphisms in NS3 and NS5A was 19% and 16%, respectively, and was seen with similar frequency in the simplified and standard arms (Supplementary Table 6). The most common NS5A polymorphisms were at positions 28 and 30. The prevalence of the Y93H/N variant was 3% in the simplified arm and 3% in the standard arm (Supplementary Table 6). Among participants with HCV genotype 3, the prevalence of the A30K variant was 2% (5/253) in the simplified arm and 1% (1/127) in the standard arm.

Among all participants enrolled, 99% (simplified arm, 98%; standard arm, 100%) completed their treatment course. Of the four participants in the simplified arm who did not complete treatment, two discontinued treatment (both within week 1), one due to an adverse event and one unwilling to continue, and two were lost to follow up on treatment (Table 2). Overall, 96% of participants were ≥95% adherent to the prescribed treatment course (simplified arm, 95%; standard arm, 98%; different between arms, -3.2%, 95%CI -6.6%, 0.2%) (Table 2).

In the intention-to-treat population (n=380), SVR12 was 92% (233/253; 95% CI 88%, 95%) in the simplified arm and 95% (121/127; 95%CI 90%, 98%) in the standard arm (difference between arms, -3.2%, 95%CI -8.2%, 1.8%) (Table 3, Figure 3). Thus, non-inferiority of the simplified arm to the standard arm was not shown, with the 95% lower confidence bound for the difference in SVR12 rates falling below -6% (-8.2%).

In the modified intention-to-treat population (n=364), excluding participants who died (n=1), were lost to follow up (n=14), or had missing HCV RNA results (n=1; unable to perform phlebotomy due to difficult venous access), SVR12 was 97% (233/241; 95%CI 94%, 99%) in the simplified arm and 98% (121/123; 95%CI, 94%, 100%) in the standard arm (difference between arms, -1.7%; 95%CI -4.9%, 1.5%) (Table 3).

In the per-protocol population (n=362), excluding participants who died (n=1), discontinued treatment (n=2), were lost to follow up (n=14) or had missing HCV RNA results (n=1), SVR12 was 97% (233/239; 95%CI 95%, 99%) in the simplified arm and 98% (121/123; 95%CI 94%, 100%) in the standard arm (difference between arms, -0.9%; 95%CI -3.9%, 2.1%) (Table 3).

The proportion with SVR12 (including 95% CI) stratified by key characteristics is shown in the Supplementary Material (Supplementary Table 8a, 8b). In the intention-to-treat population, SVR12 was higher among participants with genotype 1 (96%) as compared to those with non-genotype 1 infection (91%; p=0.03; Figure 3); SVR was 91% among participants with genotype 3. In the per-protocol population, SVR12 was similar among participants with genotype 1 (99%) as compared to those with non-genotype 1 infection (97%; p=0.12); SVR12 was 97% among participants with genotype 3. In the intention-to-treat population, SVR12 was higher among participants who were ≥95% adherent to therapy (345/366, 94%) as compared to those <95% adherent to therapy (9/14, 64%; p<0.001). Of the five non-adherent participants without an SVR12, two were early treatment discontinuations and three were lost to follow-up.

Overall, 26 participants did not achieve SVR12 (simplified arm, 20/253; standard arm, 6/127; Table 3), with the majority related to loss to follow up. There were eight cases of virological failure, including six (2.4%) in the simplified arm and two (1.6%) in the standard arm (Table 3). All participants with virological failure were ≥95% adherent to treatment. Further details on participants with virologic failure are provided in the Supplementary Material (Supplementary Tables 9a, 9b).

There were 14 participants lost to follow-up, 4 (3%) in the standard arm and 10 (4%) in the simplified arm. No baseline factors were significantly associated with lost to follow-up, although the rate was higher among those aged less than 50 years (6%) compared to older participants (2%) (Supplementary Table 10). Of note, among study participants lost to follow-up (n=14) or without SVR12 assessment (n=1), adherence reporting was available in 13 participants and was reported as above 95% in all.

Of the 380 participants enrolled, one participant (<1%) discontinued treatment prematurely because of an adverse event (simplified arm, 1/253; standard arm, 0/127) (Table 4). Overall, 53% of participants experienced at least one adverse event (simplified arm, 133/253; standard arm, 70/127), of which the majority were of mild to moderate severity (Table 4). The most common adverse events were fatigue, headache and nausea, with similar rates in the simplified and standard arms (Table 4). Three participants (1%; simplified arm, 3/253; standard arm, 0/127) experienced a treatment emergent serious adverse event; none was deemed related to treatment (Supplementary Table 12). One participant died after post-treatment week four due to lung adenocarcinoma.

Adverse event reporting was similar across arms, despite the additional clinic-based contact in the standard arm. Among all treatment-emergent adverse events reported in the simplified arm (n=294), most were reported by phone at week 4 (64%; n=188) or week 8 (20%; n=60). Among all treatment-emergent adverse events reported in the standard arm (n=192), most were reported by phone at week 4 (59%; n=114) or week 8 (17%; n=33); a minority were reported at scheduled clinic visits (clinic visit week 4, 13%, n=25; clinic visit week 8, 5%, n=9).

Participants underwent unscheduled reviews during the study (in addition to protocol mandated clinic visits or phone contact) with similar frequency in the simplified arm (8%; 20/253) as compared with the standard arm (6%; 8/127)(p=0.68), of which only a small number presented for additional review on treatment (simplified arm 4%, 11/253; standard arm 2%, 3/127; Supplementary Table 15).

DISCUSSION

Among treatment naïve patients with chronic HCV infection and without cirrhosis, efficacy of glecaprevir-pibrentasvir for eight weeks with a simplified treatment monitoring schedule did not achieve non-inferiority in comparison to a standard treatment monitoring schedule. In the intention-to-treat population, the sustained virological response was 92% in the simplified arm and 95% in the standard arm. The lower sustained virological response in the simplified arm did not relate to virological failure (simplified arm, 2.4%; standard arm 1.6%). A higher proportion with non-virological failure in the simplified arm (5.5%) compared with the standard arm (3.1%) contributed to the difference in efficacy, including early treatment discontinuations in two participants, one death, and a marginally higher loss to follow-up (4.3% versus 3.1%). Safety was comparable across both arms. These findings suggest that for many patients, particularly those without cirrhosis or adherence concerns, a simplified treatment monitoring schedule may be appropriate. Equally, the findings highlight the need for careful selection of patients for simplified treatment monitoring and the need to optimise post-treatment follow-up.

A per-protocol sustained virological response of 97%-98% across the study arms is consistent with high efficacy of glecaprevir–pibrentasvir for eight weeks demonstrated in phase 3 clinical trials (95%-99%).[9] The lower intention-to-treat sustained virological response in SMART-C (92%-95%) is attributed to a higher loss to follow-up, with recruitment into this investigator-initiated trial through a large network of tertiary and primary care sites. The majority of those lost to follow-up post-treatment (n=14) had reported high adherence during treatment, and thus may have been cured. There were no baseline factors associated with loss to follow-up, although the power to detect such associations was limited by the small sub-population.

A lack of non-inferiority in comparison of sustained virological response between simplified and standard arms was observed, with a difference in efficacy of -3.2% (95%CI -8.2%, 1.8%). The study sample was determined, based on an expected sustained virological response of 96% and a non-inferiority margin of 6%. This primary endpoint difference in intention-to-treat efficacy may reflect a true decrement in treatment outcome due to the simplified monitoring approach, or alternatively be a limitation of the study power (sample size provided 80% power to determine non-inferiority).

A simplified on-treatment monitoring schedule, with nurse phone contact at week four and week eight (end of treatment) and no face-to-face clinic visits or laboratory assessments, was safe and associated with high treatment adherence. Adverse event and adherence reporting were standardised across the randomised arms, with all study participants reporting via study nurse phone calls at week four and eight. Based on this reporting, adverse events were comparable across the study arms, in terms of overall adverse event occurrence (simplified arm, 53%; standard arm, 55%), pattern of adverse events, and serious adverse events (simplified arm, 1%; standard arm, 0%).

Adherence to glecaprevir-pibrentasvir (taken as three co-formulated pills once-daily) was high in both arms (≥95% adherent to prescribed treatment course; simplified arm, 95%; standard arm, 98%). The absence of a week four clinical visit and virological assessment in the simplified arm had limited impact on treatment adherence. The proportion of participants missing at least one dose by week 4 was higher in the simplified (10%) compared to standard (3%) arm, although this measure was similar by week 8 (12% versus 11%). Furthermore, the SVR in those missing at least one dose by week 4 in the simplified arm was high (100%), consistent with most of these participants missing only one dose. The potency and

predictability of direct-acting antiviral therapy means a vast majority of patients have either undetectable or very low-level HCV RNA at week four. Early virological assessment has therefore been considered more important for monitoring of treatment adherence.

The eligibility criteria for SMART-C highlight the need for careful clinical assessment, including discussion of adherence support needs, prior to recommending a simplified monitoring schedule. For example, people who reported injecting drug use within six months of screening were not eligible for enrolment due to their generally enhanced support needs. We have undertaken clinical trials of direct-acting antiviral therapy among people who inject drugs, that have demonstrated high adherence and efficacy, but these trials have incorporated weekly clinic visits during treatment.[19] Adherence rates decline with increasing treatment complexity, longer duration of therapy, and higher pill burden,[20-25] highlighting the importance of simple HCV treatment strategies to optimise adherence and outcomes.

Some HCV treatment guidelines have already incorporated optional on-treatment virological monitoring. The European Association for the Study of the Liver (EASL) recommends that among patients receiving DAA therapy, HCV RNA (or HCV core antigen) and ALT should be measured at baseline and at post-treatment week 12 (or 24) to assess treatment efficacy (level of evidence: A1) and safety (level of evidence: B1), respectively.[26] Indeed, the current EASL guidelines push the boundary further and suggest that "given the high SVR12 rates expected with these regimens across all groups of patients if adherent, checking SVR12 12 weeks after the end of treatment is dispensable (level of evidence: B1/B2)".[26] The American Association for the Study for the Liver (AASLD) guidelines remain more conservative, recommending on-treatment laboratory assessments of efficacy (HCV RNA) and safety (liver and renal function; level of evidence: B1).[27]

The lack of non-inferiority in the SMART-C study provides some caution in relation to the EASL guidelines regarding simplified on-treatment monitoring. The possibility remains that some patients, even within the restricted eligibility of the SMART-C study, may have benefited from standard on-treatment monitoring. We also believe that documentation of SVR12 remains an important component of HCV therapeutic management, despite a low virological failure rate. The SMART-C study incorporated a nurse phone contact at week four and eight (end-of-treatment). This contact may have assisted treatment adherence and post-treatment follow-up, therefore our findings should not be extrapolated to situations without this form of patient contact.

The SMART-C study has some limitations that should be considered. First, although the protocol excluded patients whom the clinician judged to have treatment adherence concerns, a standardized adherence assessment tool was not incorporated within the study. Second, the study population was restricted to patients who were HCV treatment naïve, without cirrhosis, and recruited in high-income countries, largely through tertiary clinics. Further studies of simplified monitoring are required in different settings and populations. Importantly, the MINMON (clinicaltrials.gov; NCT03512210) single-arm trial is evaluating a simplified monitoring schedule for sofosbuvir-velpatasvir in the United States and several low- and middle-income countries. Finally, a cost-effectiveness evaluation has not been undertaken to date. Clinical care cost reductions through a simplified monitoring schedule could be offset if the sustained virological response is reduced, even by a small margin.

Additional aspects of simplified monitoring that could be evaluated, are the need for phone contact on-treatment, and mechanisms to enhance post-treatment follow-up, including self-

collection and posting of samples (such as dried blood spots) for SVR12 assessment. A key aspect of simplified monitoring trials is provision of the full course of therapy at treatment initiation, eight weeks therapy with glecaprevir-pibrentasvir for SMART-C and 12 weeks therapy with sofosbuvir-velpatasvir for MINMON. Incorporation of this simplified aspect may require regulatory changes in relation to pharmacy dispensing in different countries.

In conclusion, the SMART-C study has demonstrated high adherence, high tolerability, and high treatment efficacy with an eight-week regimen of glecaprevir-pibrentasvir in patients with chronic HCV who are treatment naïve and without cirrhosis. Although the comparison of simplified to standard treatment monitoring did not achieve non-inferiority, we believe that simplified monitoring can be recommended for many patients with chronic HCV, following careful individualised clinical assessment, including adherence support needs. Progress towards achieving the WHO HCV elimination 2030 goals should be enhanced through greater simplification of DAA treatment and monitoring.

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Table 1. Baseline demographic, clinical and virological characteristics in the intention-to-treat population

	Total study population N=380	Standard monitoring arm N=127	Simplified monitoring arm N=253
Age, median (range)	51 (22, 79)	50 (24, 79)	52 (22, 73)
Gender, n (%)			
Male	229 (60)	72 (57)	157 (62)
Female	149 (39)	53 (42)	96 (38)
Transgender	2 (1)	2 (2)	0
Ethnicity, n (%)			
White	291 (77)	97 (76)	194 (77)
Asian	34 (9)	12 (9)	22 (9)
Black	20 (5)	7 (6)	13 (5)
Other	35 (9)	11 (9)	24 (9)
BMI, median (range)	25.0 (17.8, 51.5)	24.7 (18.2, 51.5)	25.3 (17.8, 41.7)
HCV genotype, n (%)			
Genotype 1	179 (47)	61 (48)	118 (47)
1a	124	47	77
1b	51	14	37
1, not specified	4	0	4
Genotype 2	52 (14)	17 (13)	35 (14)
Genotype 3	121 (32)	41 (32)	80 (32)
Genotype 4	18 (5)	4 (3)	14 (6)
Genotype 5	1 (<1)	1 (1)	0
Genotype 6	8 (2)	3 (2)	5 (2)
Genotype indeterminate	1 (<1)	0	1 (<1)
HCV RNA			
Log_{10}, median (range)	6.28 (2.49, 7.74)	6.29 (2.85, 7.71)	6.27 (2.49, 7.74)
Fibrosis stage, n (%) *			
No or mild fibrosis (F0/F1)	283 (74)	93 (73)	190 (75)
Moderate fibrosis (F2)	78 (21)	29 (23)	49 (19)
Severe fibrosis (F3	19 (5)	5 (4)	14 (6)
HIV infection, n (%)	27 (7)	13 (10)	14 (6)
CD4 count (10^6/L), median (range)	698 (372, 984)	652 (372, 984)	698 (446, 863)
HIV viral load ≤50 at screening, n (%)	24 (89)	12 (92)	12 (86)
On antiretroviral therapy, n (%)	27 (100)	13 (100)	14 (100)
Opioid substitution therapy, n (%)	38 (10)	17 (13)	21 (8)

*Categorisation of fibrosis stage: No or mild fibrosis (F0/F1): LSM <7.1kPa or APRI <0.5; significant fibrosis (F2): LSM 7.1-9.4kPa or APRI 0.5–1.0; severe fibrosis (F3): LSM 9.5-12.4kPa

Table 2. Treatment completion, adherence and visit attendance in the intention-to-treat population

	Total study population N=380	Standard monitoring arm N=127	Simplified monitoring arm N=253
Treatment completion			
Commenced treatment, n (%)	380 (100%)	127 (100%)	253 (100%)
Completed allocated treatment course, n (%)	376 (99%)	127 (100%)	249 (98%)
Discontinued treatment, n (%)	2 (<1%)	0	2 (1%)
Adverse event [1]	1	0	1
Non-compliance [2]	1	0	1
Loss to follow up on treatment, n (%) [3]	2 (<1%)	0	2 (1%)
Visit attendance			
Week four, n (%)			
Phone contact	352 (93%)	113 (89%)	239 (94%)
Clinic visit	NA	127 (100%)	NA
Week eight, n (%)			
Phone contact	348 (92%)	114 (90%)	234 (92%)
Clinic visit	NA	124 (98%)	
Adherence			
Overall adherence, n (%)			
≥95%	366 (96%)	125 (98%)	241 (95%)
≥90%	370 (97%)	126 (99%)	244 (96%)
Missed doses, by treatment period [4]			
Week 0 – 4			
Any missed doses, n (%)	28 (5%)	3 (3%)	25 (10%)
Number of missed doses, median (range) [5]	1 (1, 5)	1 (1, 1)	1 (1, 5)
Week 5 – 8			
Any missed doses, n (%)	41 (12%)	13 (11%)	28 (12%)
Number of missed doses, median (range)	1 (1, 13)	1 (1, 3)	1, (1, 13)

1. Participant discontinued treatment after day 5 due to an adverse event (gastrointestinal disorder, mild)
2. Participant discontinued treated after day 2; reason for discontinuation unclear
3. Including one participant who was incarcerated while on treatment
4. Assessed by self-report during phone contact at week 4 (n=352) and week 8 (n=348)
5. Median number of missed doses among those reporting 1 or more missed doses

Abbreviation: NA, not applicable

Table 3. Treatment outcomes, primary and secondary efficacy endpoints

Outcome	Standard monitoring arm N (%)	Simplified monitoring arm N (%)	Difference between arms (95% CI)
Intention to treat population	**N=127**	**N=253**	
SVR12, n (%)	121 (95%)	233 (92%)	-3.2% (-8.2%, 1.8%)
Virologic failure, n (%)	2 (2%)	6 (2%)	0.8% (-2.1%, 3.7%)
On-treatment failure	0	NA	
Post-treatment relapse	2	NA	
Failure for other reasons, n (%)	4 (3%)	14 (6%)	-2.2 % (-6.3%, 2.0%)
Death	0	1 (<1%)	
Discontinuation	0	2 (1%)	
Loss to follow up or missing HCV RNA[1]	4 (3%)	11 (4%)	
Modified intention to treat population	**N=123**	**N=241**	
SVR12, n (%)	121 (98%)	233 (96%)	-1.7% (-4.9%, 1.5%)
Virologic failure, n (%)	2 (2%)	6 (2%)	
On-treatment failure	0	NA	
Post-treatment relapse	2	NA	
Failure for other reasons, n (%)			
Discontinuation	0	2 (1%)	
Per-protocol population	**N=123**	**N=239**	
SVR12, n (%)	121 (98%)	233 (97%)	-0.9% (-3.9%, 2.1%)
Virologic failure, n (%)	2 (2%)	6 (2%)	
On-treatment failure	0	NA	
Post-treatment relapse	2	NA	

1. Missing HCV RNA: One participant in the simplified arm completed study follow up and attended clinical review at post-treatment week 12, but given difficult venous access, phlebotomy was unsuccessful.

Table 4. Safety parameters, adverse events, and treatment discontinuation in the intention-to-treat population^

Adverse events	Standard monitoring arm N=127	Simplified monitoring arm N=253
Participants reporting any TEAE up to 30 days after last dose, n (%)	70 (55%)	133 (53%)
Grades 1-2, n (%)	69 (54%)	131 (52%)
Grade 3, n (%)	1 (1%)	2 (1%)
Grade 4, n (%)	0	0
Participants reporting treatment-related TEAE up to 30 days after last dose, n (%)	50 (39%)	86 (34%)
Grades 1-2, n (%)	50 (39%)	85 (34%)
Grade 3, n (%)	0	1 (<1%)
Grade 4, n (%)	0	0
Serious TEAE, n (%)	0	3 (1%) *
Treatment-related serious TEAE, n (%)	0	0
Treatment discontinuation due to adverse event, n (%)	0	1 (<1%)
Death, n (%)	0	1 (<1%) ‡
Adverse events		
Common (>5% of study population), n (%)		
Fatigue	30 (14%)	52 (15%)
Headache	26 (12%)	43 (13%)
Nausea	25 (12%)	17 (5%)
Unscheduled clinic visits or phone contact		
Any timepoint following enrolment, n (%)	8 (6%)	20 (8%)
On treatment, n (%)	3 (2%)	11 (4%)

^ The intention-to-treat population (full analysis set) and the safety population were the same.

* These events were deemed by the investigators as having no reasonable possibility of being related to the trial drugs. Additional information on serious adverse events is provided in the Supplementary Material.

‡ The participant died after post-treatment week 4 from lung adenocarcinoma (unrelated to the study drug or study conduct).

Abbreviation: TEAE, treatment emergent adverse event

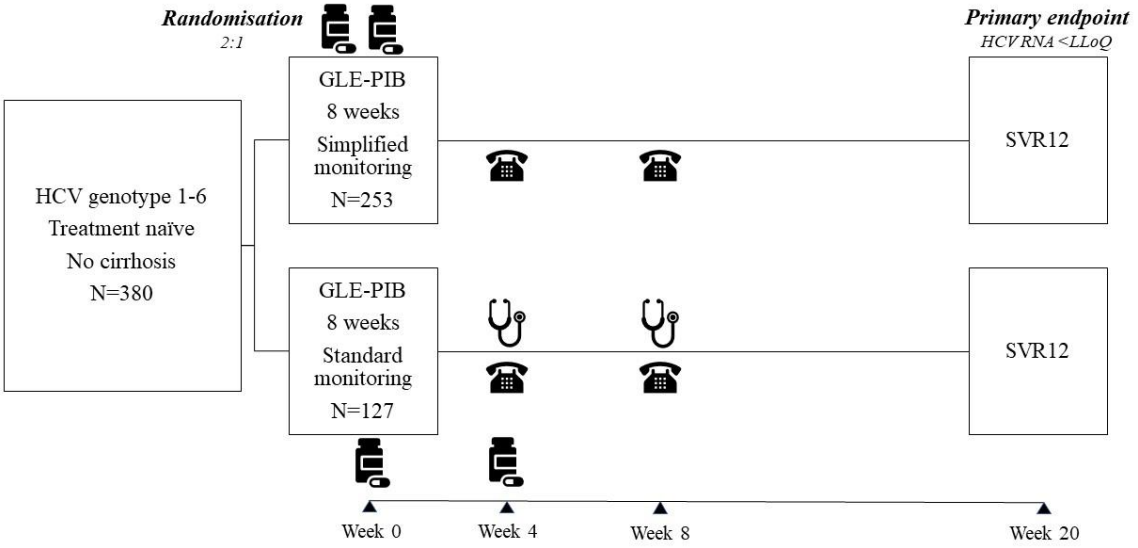

Figure 1. Study design

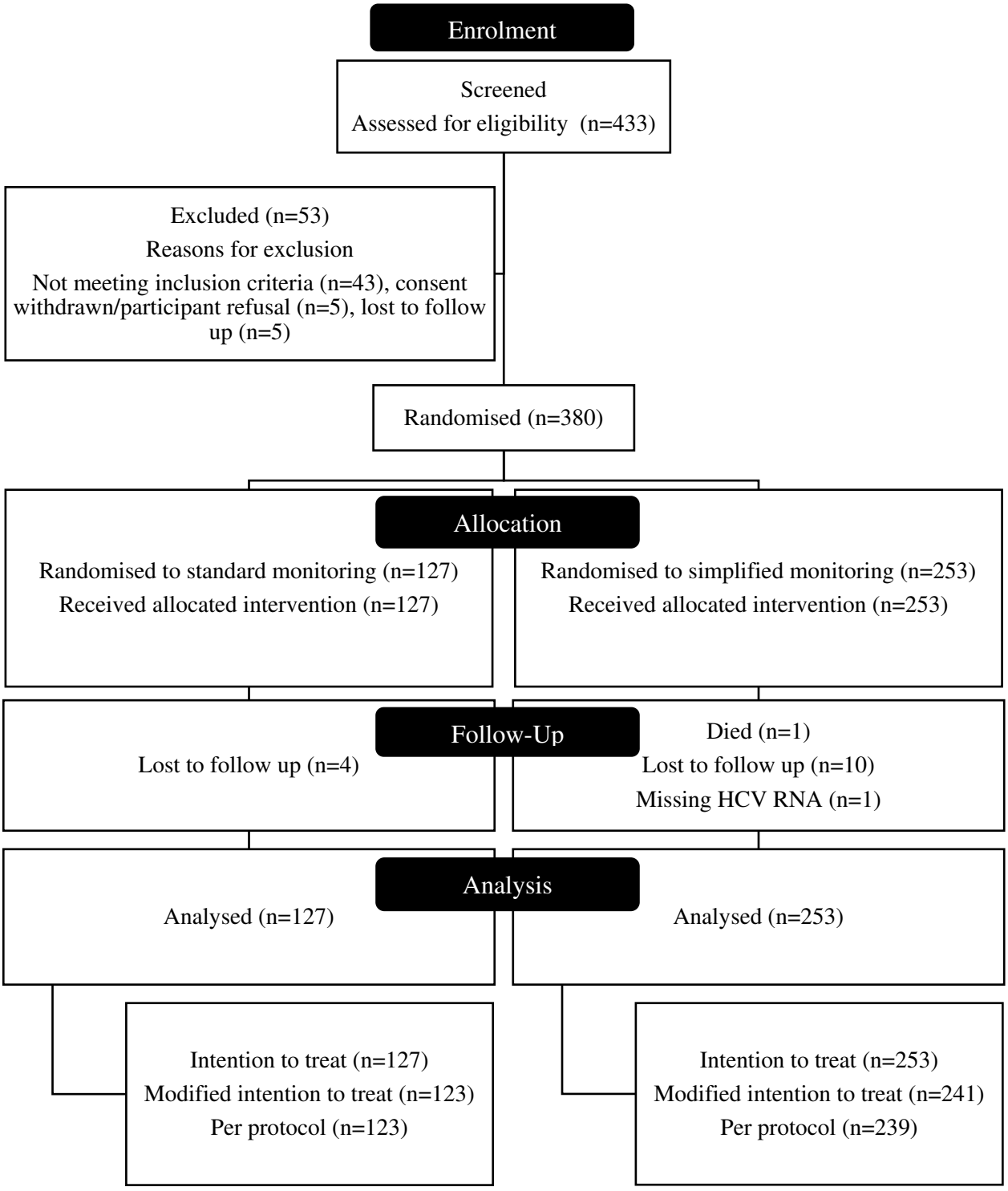

Figure 2. Participant disposition

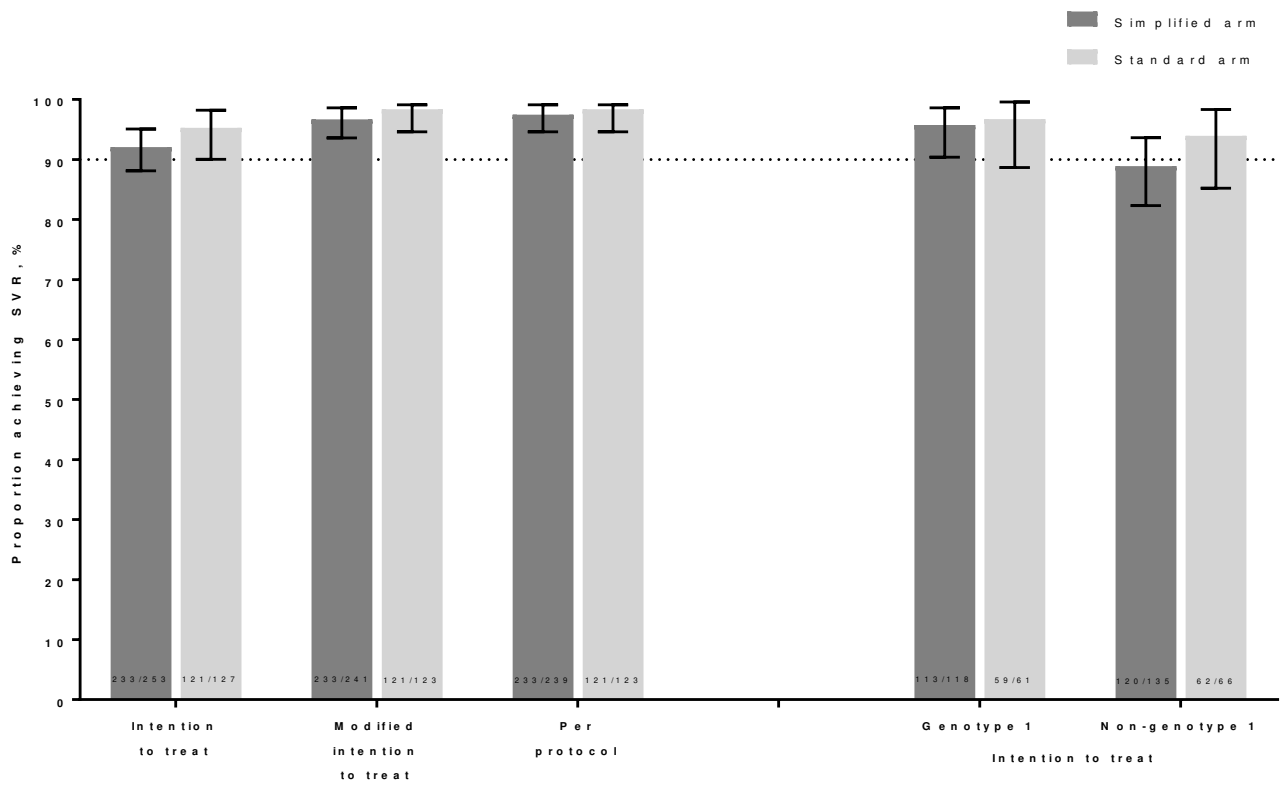

Figure 3. Efficacy in the intention-to-treat and per-protocol population

Figure Legends

Fig 1. Study design

Treatment-naïve adults with chronic HCV and without cirrhosis were randomly assigned (2:1) to receive glecaprevir-pibrentasvir 300mg-120mg for eight weeks administered with a simplified or standard monitoring strategy. In the standard arm, scheduled face-to-face clinic study visits were undertaken at baseline, treatment weeks four and eight (end of treatment), and post-treatment week 12. In the simplified arm, scheduled face-to-face clinic study visits were undertaken at baseline and post-treatment week 12. In both the standard and simplified arms, phone contact was initiated by the study nurse at weeks four and eight (end of treatment). Study drug dispensing occurred at baseline and week 4 in the standard arm, and at baseline only in the simplified arm.

Abbreviations: GLE-PIB, glecaprevir-pibrentasvir; SVR12, sustained virological response at 12 weeks post treatment

Fig 2. Participant disposition

The number of participants screened (n=433), randomised (n=380) and analysed (intention-to-treat population/full analysis set, n=380) is depicted.

Of the 53 participants who were excluded, 43 did not meet the inclusion criteria, five were lost to follow up, and five withdrew consent. Reasons for failing the inclusion criteria included 1. chronic HCV infection (n=1), 2. HCV RNA plasma ≥ 10,000 IU/ml (n=18) and 3. fibrosis stage F0-F3 (n=6). Reasons for failing the exclusion criteria included 1. history of significant co-morbid illness or decompensated liver disease (n=1), 2. abnormal laboratory parameters (n=5), 3. receipt of anti-neoplastic or immunomodulatory therapy within 6 months (n=1), 4. positive urine drug screen (n=10) and 5. injecting drug use within 6 months (n=1)

Fig 3. Efficacy in the intention-to-treat and per-protocol population

Dotted line at 90% representing the lower bound of the 95%CI for the standard (control) arm.